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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JUNE, 1930

ORIGINAL ARTICLES.

MYXEDEMA DURING THE ADMINISTRATION OF IODIN IN EXOPHTHALMIC GOITER.*

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With the exception of the case reported by Haines[1] and referred to by Plummer,[2] we know of no instance of typical myxedema attributed to the administration of iodin.

In a previous study of low basal metabolism following thyrotoxicosis[3,4,5] we observed that the temporary administration of iodin sometimes produced a temporary low metabolic rate.[3] In none of these instances, however, was there sufficient clinical evidence to justify a diagnosis of myxedema. The data suggested that in some cases the low metabolism might be normal for the patients, while in others it might represent an underfunction of the thyroid which did not last long enough to become evident upon physical examination. About a year and a half ago, one of the patients reported in this study returned to the clinic after a considerable absence com-

* This study was aided in part by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

plaining that her eyes had not completely returned to their pregoiter size. Otherwise she appeared normal. For her persistent exophthalmos she was given iodin. During each of two courses of this medication her basal metabolism slowly dropped to a low level, and, in association with this, she developed typical myxedema. This cleared up promptly and her basal metabolic rate rose to normal either when iodin was omitted, or when iodin was continued and desiccated thyroid given in addition.

In two other patients myxedema was associated with the postoperative administration of iodin. In one, iodin appeared to be the cause of the myxedema. In the other, it accentuated a mild postoperative myxedema. In the latter patient before operation, and in another patient who has never been operated on, iodin produced a syndrome suggestive of myxedema.

Data. The data on the 4 cases are given in histories and figures.*

In the following patient there is no doubt that typical myxedema was produced at least twice by the postoperative administration of iodin:

Case reports. CASE I.—(Fig. 1.) Lab. No. 3543. Miss B. B., a Jewish housemaid aged eighteen years, entered this hospital October 8, 1925, having typical exophthalmic goiter of moderate severity with marked exophthalmos. Her basal metabolism ranged from +37 to +44. On Lugol's solution it promptly fell to +14 and she improved symptomatically. October 22 a subtotal thyroidectomy was performed. November 5, when her metabolism was −9, Lugol's solution was started in a dose of 8 drops daily. During its administration her metabolism gradually fell until on January 6, 1926, it was −25. At this time her face was round and slightly puffy and she appeared a little slowed up. The evidence was not considered adequate, however, to make a diagnosis of myxedema. Iodin was then omitted. Her metabolism rose to standard normal and for the next ten months, for the most part on combined iodin and thyroid medication, maintained the course shown in Fig. 1.

She was not seen subsequently for about a year. On returning to the hospital December 28, 1927, her basal metabolic rate was +25 and this raised the question of residual thyrotoxicosis. On frequent successive tests, however, her metabolism, without medication, fell to normal. As far as could be determined clinically she had no thyrotoxicosis. She was a very active individual and had a moderate residual bilateral exophthalmos (more on the right than on the left) and slight lid lag on the right, but there was no tremor, excess sweating, weakness or undue nervousness. There was a pea-sized nodule of palpable thyroid tissue on the left side of her neck.

On January 26, 1928, 2 drops of Lugol's solution daily was started, in order to try its effect in reducing the exophthalmos. The first subsequent low basal metabolism (−17) was noted April 12. Her voice had become somewhat hoarse, and about this time she began to feel a little listless and sleepy in the daytime. April 26 (basal metabolic rate still −17) her skin was noted to be a little rough and dry. By May 10 her metabolism was −25 and the myxedema was typical. She was markedly apathetic, drowsy and slowed up, and her muscles tired very easily on exertion. She had gained 4 kg. in weight since starting iodin, her face had become puffy and her skin

* All basal-metabolism determinations were made with the Benedict-Roth apparatus, and Aub-Du Bois standards were used in the calculations.

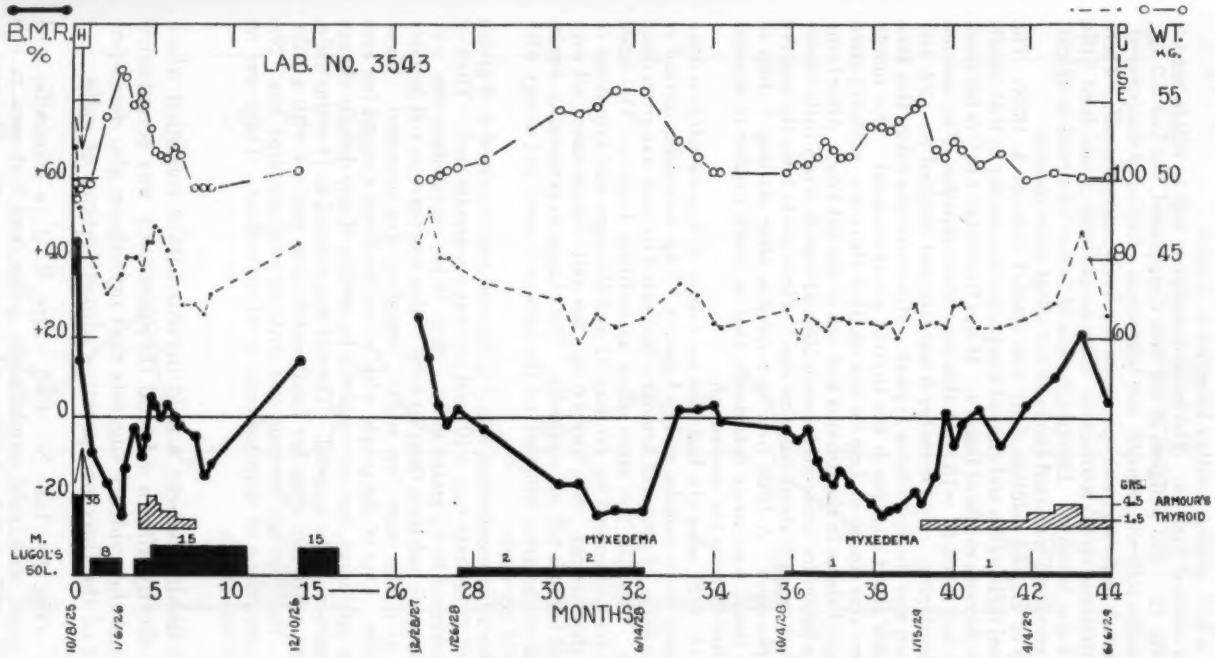

FIG. 1.—Case I. The development of typical myxedema during administration of iodin, two and a half and again three years after subtotal thyroidectomy (arrow) for exophthalmic goiter. At the time of the first low basal metabolism on iodin shortly after operation the clinical evidence was not sufficient to make a diagnosis of myxedema. In this and subsequent charts, the black areas denote periods of treatment with compound solution of iodin and the cross-hatched areas, periods of treatment with Armour's desiccated thyroid.

harsh and dry. Her speech was slow and thick and her voice hoarse. She was extremely sensitive to cold. She continued thus for about another month and a half, gaining another kilogram in weight.

Iodin was omitted June 14. The basal metabolism rose to within normal limits by July 12. The puffiness of her face disappeared, she lost 3.2 kg., her skin became soft and smooth, her hoarseness practically disappeared, she talked much faster and was once more her lively, energetic self. There were no symptoms of thyrotoxicosis. Her exophthalmos had been little affected by iodin, however. Except for a loss of 2 more kilograms in weight, her clinical condition remained the same for about three months.

One drop of Lugol's solution daily was started October 4, 1928. The effect on basal metabolism and clinical symptoms was similar to that resulting from the previous course of Lugol's. It was November 1 before her basal metabolism had fallen to −15. At this time the symptoms of myxedema were just developing. By December 6 her rate had dropped to −22, and not until then was the myxedema typical. More care was taken this time to make notes about changes in the thyroid gland remnant. One month after the previous course of Lugol's was omitted there was a cherry-sized mass of thyroid tissue in the isthmus and one in the left lobe. After being on Lugol's solution for three weeks, each thyroid nodule was a little harder and firmer but was still about the same size. Three weeks later the nodules were only pea-sized. A little over two months after starting 1 drop of Lugol's the tissue was barely detectable, that is, much smaller in amount than just after starting the medication.

January 15, 1929, after she had been on 1 drop of Lugol's solution daily for a little over three months, and had gained 4.7 kg. in weight, instead of omitting the iodin, 1½ grains of Armour's desiccated thyroid was given daily in addition. This had the same effect as omitting Lugol's. The basal metabolism rose to normal by January 31 and the signs and symptoms of myxedema disappeared. She lost 3.6 kg., her skin desquamated all over her body and her hair fell out markedly. The change in personality was so striking that her mistress remarked on the increased speed and energy with which she did her work.

April 4 when her metabolism was +3, thyroid was increased to 3 grains daily. April 25 her rate was +10, and she was apparently well. Thyroid was then increased to 4½ grains daily. May 16 her metabolism was +21 and her pulse rate had risen from 69 to 87. She was nervous and irritable and acted as if she were "on edge." Sweating was increased. There was no tremor. One of the people with whom she lived thought her eyes protruded a little more, but we could not be certain of any definite change when she was seen in the hospital. Thyroid was reduced to 1½ grains daily. June 6, 1929, when last seen, her basal metabolism was +4 with a pulse rate of 66. She was less nervous and irritable and perspired less. She showed no symptoms of thyrotoxicosis or of myxedema. There was no palpable thyroid tissue.

In the following patient a mild myxedematous condition which developed shortly after a subtotal thyroidectomy was accentuated by iodin, and the evidence suggests that myxedema also developed during one of the three preoperative administrations of iodin:

CASE II.—(Fig. 2.) Lab. No. 4675. Mrs. E. C., a housewife, aged thirty-five years, with mild exophthalmic goiter, was first seen in this clinic April 7, 1927, when her basal metabolic rate was +22. She was nervous, fatigued easily, had palpitation and was losing weight; her skin was warm and moist and showed marked dermographia; she had a tremor

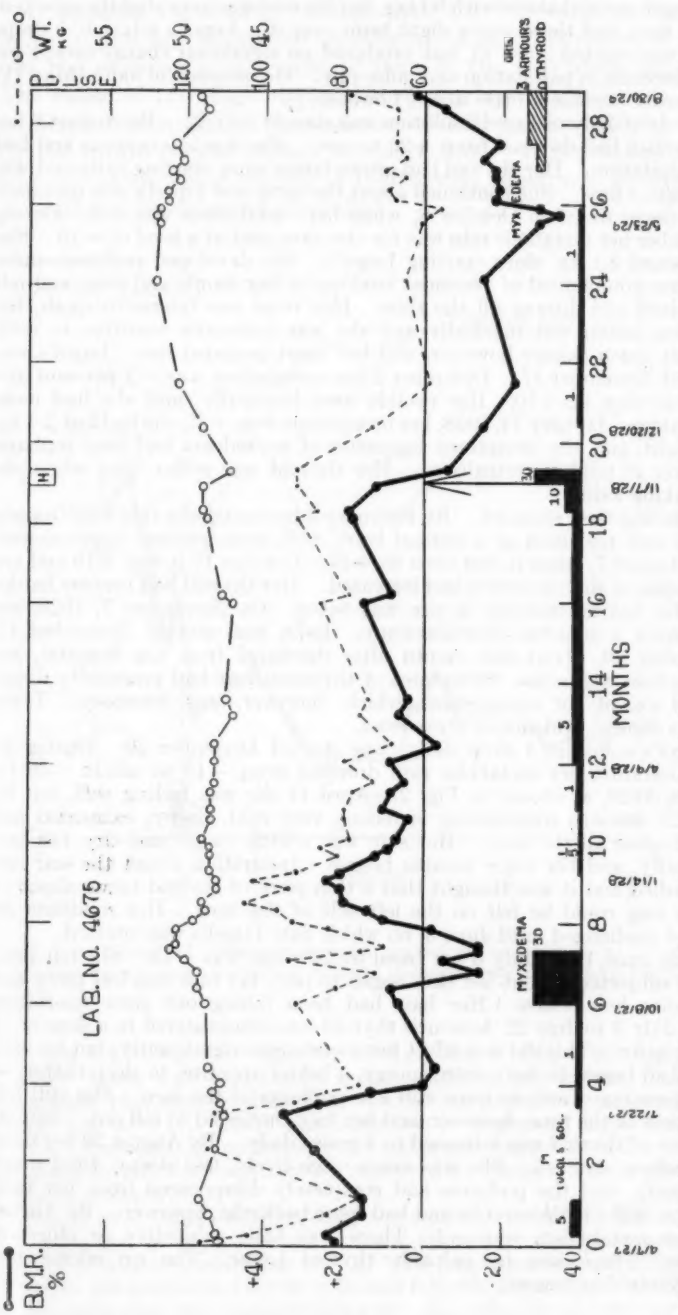

FIG. 2.—Case II. The development of myxedema during administration of iodin in a patient with exophthalmic goiter before a subtotal thyroidectomy (arrow) and the accentuation of myxedema during iodin administration after operation.

and slight exophthalmos with lid lag; her thyroid was very slightly enlarged, rather firm, and there was a slight bruit over it. Lugol's solution, 5 drops daily, was started April 13, but produced no significant change except for some decrease in palpitation and pulse rate. On omission of iodin (May 11) the disease became a little worse, however.

One drop daily of Lugol's solution was started July 22. By August 6 her metabolism had dropped from +26 to zero. She was less nervous and had less palpitation. Her thyroid had grown larger since starting iodin and was moderately firm. She continued about the same and Lugol's was increased to 30 drops daily on October 8, when her metabolism was +6. During November her metabolic rate was for the most part at a level of −15. She had gained 3.1 kg. since starting Lugol's. She developed puffiness under her eyes, complained of transient swelling of her hands and feet, and felt very tired and drowsy all the time. Her voice was hoarse in spells, her hair was falling out markedly and she was unusually sensitive to cold. She felt much calmer however, and her heart pounded less. Lugol's was omitted November 17. December 2 her metabolism was −2 per cent and on December 9, +10. Her eyelids were less puffy, and she had more palpitation. January 14, 1928, her metabolism was +21, she had lost 2.4 kg. in weight, and the symptoms suggestive of myxedema had been replaced by those of mild thyrotoxicosis. Her thyroid was softer than when she was taking iodin.

Iodin was then resumed. By February 3 her metabolic rate had dropped to +9 and remained at a normal level, with some clinical improvement, until August 7, when it had risen to +15. October 17 it was +19 and the symptoms of thyrotoxicosis had increased. Her thyroid had become harder on iodin but no increase in size was noted. On November 7, 1928, she underwent a subtotal thyroidectomy. Iodin was omitted November 17. December 20, about one month after discharge from the hospital, her metabolism was −15. Symptoms of thyrotoxicosis had practically disappeared except for nervousness, which, however, was decreased. There was no clinical evidence of myxedema.

Lugol's solution, 1 drop daily, was started December 20. During its administration her metabolic rate dropped from −15 to about −30 by June 3, 1929, as shown in Fig. 2. April 11 she was feeling well, but by May 23 she was complaining of feeling very cold, sleepy, exhausted and ambitionless all the time. Her skin was a little rough and dry, her face was puffy, and her voice became hoarse. Induration about the scar had diminished and it was thought that a thin piece of thyroid tissue about 1½ inches long could be felt on the left side of the neck. Her condition remained unchanged until June 3, on which date Lugol's was omitted.

From June 12 to July 3 her basal metabolism was −18. She felt little better subjectively, but her skin began to peel, her face was less puffy and her voice less hoarse. Her hair had been falling out since operation. From July 3 to July 22 Armour's thyroid was administered in a dose of 1½ grains daily. This did not affect her metabolism significantly, but by July 9 she had begun to have more energy, a better appetite, to sleep better, be less discouraged and to have still less puffiness of the face. She still felt cold most of the time, however, and her hair continued to fall out. July 22 the dose of thyroid was increased to 3 grains daily. By August 20 her basal metabolism was −5. She was much more lively, less sleepy, tired much less easily, and the puffiness had completely disappeared from her face. She was still a little nervous and had some backache, however. By August 30, her metabolism was +2. There was little subjective or objective change. There was no palpable thyroid tissue. The myxedema had completely disappeared.

It appears reasonably certain that the following patient had mild myxedema during the postoperative administration of iodin, but the evidence is less definite than in the two preceding cases. The cause of the slight depression of the basal metabolism which occurred subsequent to the omission of iodin can be explained only by the future clinical history of the patient. It is possible that it was due to an underfunction of the thyroid which was so mild that it could not be detected clinically:

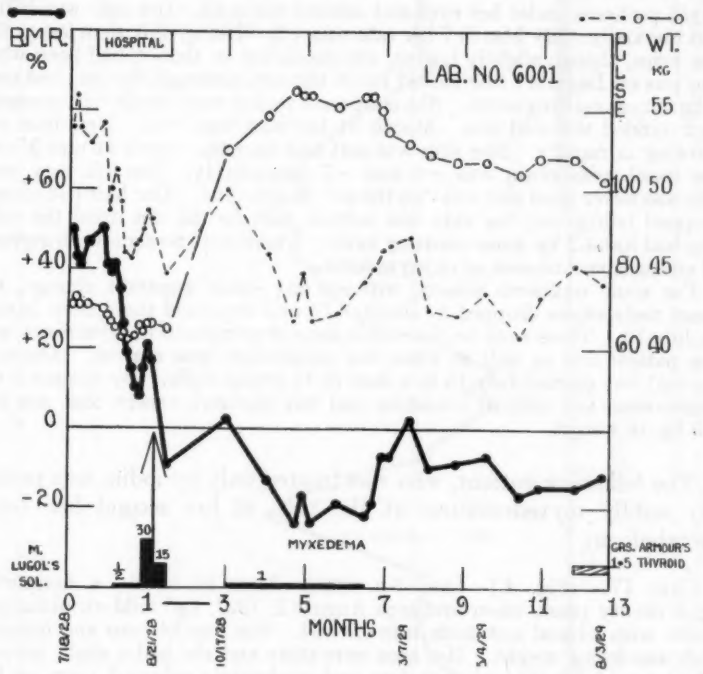

FIG. 3.—Case III. Temporary mild myxedema coincident with temporary administration of iodin, following subtotal thyroidectomy (arrow) for exophthalmic goiter.

CASE III.—(Fig. 3.) Lab. No. 6001. Miss E. M., a schoolgirl, aged sixteen years, had moderately severe exophthalmic goiter. Her basal metabolic rate responded to iodin medication pre-operatively with a fall from +50 to +17. There was coincident improvement in clinical symptoms. A subtotal thyroidectomy was performed August 21, 1928. She was discharged from the hospital much improved on September 1, at which time iodin was omitted.

One drop of Lugol's solution daily was started October 17, 1928. At this time she had no thyrotoxicosis and was apparently normal symptomatically, with a basal metabolism of +2. Her exophthalmos had disappeared, her skin was normal and her face, though full, was not puffy. By December 8 her metabolism had gradually fallen to −24. She did not have her normal

amount of energy and ambition and she minded the cold a great deal. She had gained 3.7 kg. in weight and had developed some puffiness under her eyes. Her skin was a little dry and her hair was falling out. Her voice was husky, but this may have been a result of a paralysis of the right vocal cord which was noted just after operation.

Her clinical condition continued about the same until Lugol's was omitted February 2, 1929. By February 15 her metabolism had risen to −7. For about a week she had noted a marked change in herself. She had much more energy, vivacity and ambition. Her appetite was better. She wanted to be active all the time, whereas, while on Lugol's, she was contented to sit around the house and read. She was still slightly hoarse, had slight puffiness under her eyes and minded the cold. Her hair was falling out markedly. By March 7 her rate was +2. Her eyelids were less puffy, her voice, though slightly hoarse, was much less so than it had been when she was on Lugol's. She looked much thinner, although she had lost only 3 kg. since omitting iodin. She continued to feel more lively and energetic and minded the cold less. March 21 her rate was −10. New hair was growing in rapidly. Her skin was soft and smooth. April 11 and May 4 her basal metabolism was −9 and −7 respectively. She felt very well. She was never tired and was "on the go" all the time. Her hair had almost stopped falling out, her skin was normal and she did not mind the cold. She had lost 4.2 kg. since omitting iodin. There were no signs or symptoms of either thyrotoxicosis or of myxedema.

For some unknown reason, without any other apparent change, the basal metabolism dropped to about −15 and remained there from June 1 to July 13. There were no detectable signs or symptoms of myxedema, and the patient felt as well as when the metabolism was normal. Armour's thyroid was started July 13 in a dose of 1½ grains daily. By August 3 the metabolism and clinical condition had not changed, except that she lost 1.6 kg. in weight.

The following patient, who was treated only by iodin, was probably mildly myxedematous at the time of her second low basal metabolism:

Case IV.—(Fig. 4.) Lab. No. 5004. Mrs. M. P. W., a housewife, aged twenty years, when first seen August 2, 1927, had mild exophthalmic goiter with a basal metabolic rate of +24. She was nervous and irritable and was losing weight. Her eyes were stary and she had a slight tremor. The lobes of her thyroid were firm and moderately enlarged, more on the right than on the left, and the isthmus was markedly enlarged. There was a well-marked systolic bruit over both superior thyroid arteries, more marked on the right. She had been given iodin by a local doctor, but had had none for at least one month before coming to the hospital. Lugol's solution, ½ drop daily, was started August 4. October 14 her metabolism was +10 and she had gained 2 kg., but there was no subjective change. Her goiter, after an initial enlargement on iodin, had become smaller and softer. Lugol's was omitted. Off iodin her metabolism ranged from +30 to +47. She lost about 2 kg. in weight, her skin became more moist and flushed, she was more nervous and restless and she developed some palpitation and dyspnea.

November 5, when her rate was +35, Lugol's solution was resumed, first in a dose of ½ drop daily and then 1 drop daily. By January 21, 1928, her metabolism had fallen to −14 and remained at approximately this level until February 25. She gained 6.7 kg. in weight, was much less irritable and

nervous and felt unusually energetic. She did not mind the cold. Her lower eyelids were slightly puffy, but there was no other clinical evidence suggesting thyroid underfunction. Her thyroid was just slightly enlarged and there was no bruit or thrill over it.

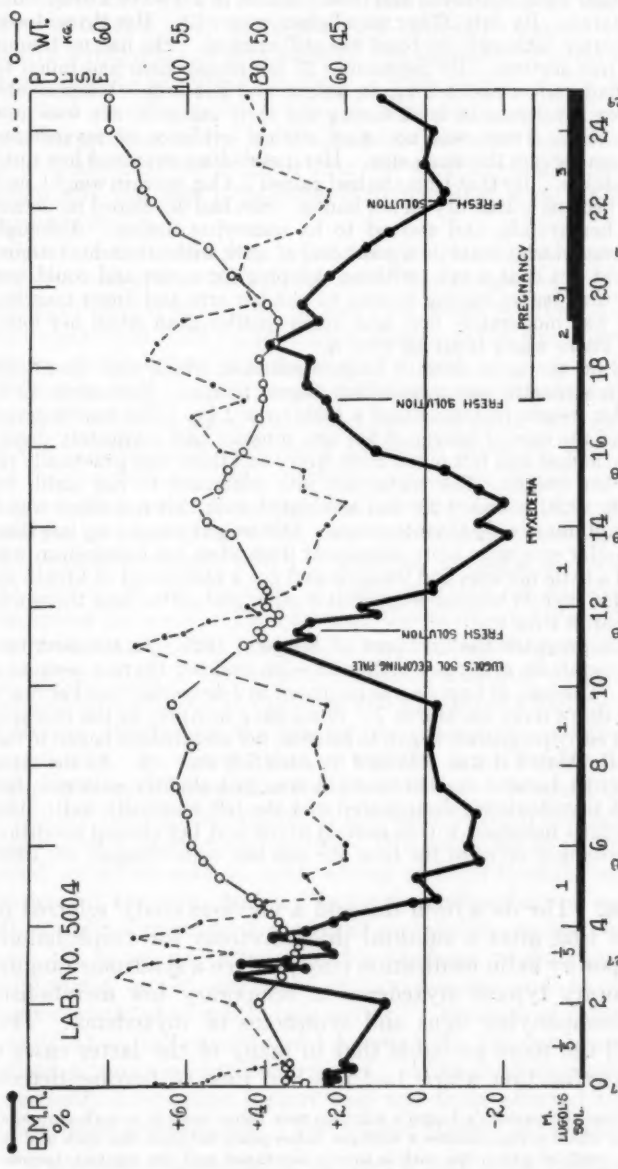

FIG. 4.—Case IV. The development of signs and symptoms suggesting mild myxedema during the second of two periods of low basal metabolism, which occurred during the continuous administration of iodin to a patient with otherwise untreated exophthalmic goiter.

While on the same dose of Lugol's solution, which solution however, was becoming much paler,* her metabolism started to rise. July 13 it was +32. Her thyroid had grown definitely larger and firmer and there was a bruit all over it, most marked at each superior pole. She had lost 4.5 kg. in weight, had a slight tremor, and her eyes were more prominent.

The old Lugol's was destroyed and fresh solution in a dose of 1 drop daily was administered. By July 27 her metabolism was +12. Her thyroid was smaller and softer, although the bruit was still marked. She had no tremor and seemed less nervous. By September 27 her metabolism had fallen to −21. She had gained about 2 kg. in weight and felt well. Whereas she had been very intolerant of heat during the early summer, she was now sensitive to cold. There was no other clinical evidence of myxedema. Her thyroid was about the same size. Her metabolism remained low until the end of October. By that time she had gained 2.4 kg. more in weight, and her skin had become a little dry on her hands. She had developed moderate puffiness of her eyelids, and seemed to be somewhat listless. Although naturally a woman who could do a great deal of work without undue fatigue, she then could not beat a cake without stopping for a rest and could sew only a short time before having to stop to rest her arm and finger muscles. Her thyroid was moderately firm and much smaller than when her iodin was weak. There was a bruit all over it.

While still on the same dose of Lugol's solution, which was essentially unchanged in strength, her metabolism began to rise. November 15 it was −5. Her weight had decreased a little over 2 kg. The numbness of her hands and the ease of fatigue of her arm muscles had completely disappeared. She looked and felt much more lively and there was practically no puffiness of her eyelids. Her metabolic rate continued to rise until, by December 18, 1928, it was +23, and associated with this rise there was a return of symptoms of mild thyrotoxicosis. Her weight was 4.2 kg. less than in October. Her eyes were more prominent than when her metabolism was low, she was a little nervous and irritable and got a little short of breath on exertion. Her thyroid became somewhat smaller and softer, and there was still a slight bruit over it.

She became pregnant the first part of January, 1929. In the next two months her metabolic rate rose further to +39, and her thyroid became a little larger. The dose of Lugol's was increased to 2 drops daily on February 21, and to 3 drops daily on March 7. Some time in April, as the morning nausea of her early pregnancy began to subside, her metabolism began to fall gradually. By May 2 it was +15 and by June 6 it was −4. At the same time her thyroid became smaller, until it was just slightly enlarged, her symptoms of thyrotoxicosis disappeared and she felt unusually well. Her basal metabolism remained within normal limits and her clinical condition remained unchanged up until the time she was last seen—August 26, 1929.

Discussion. The data from this and a previous study[3] referred to above show that after a subtotal thyroidectomy for exophthalmic goiter, temporary iodin medication may produce a syndrome ranging from temporary typical myxedema to temporary low metabolism without accompanying signs and symptoms of myxedema. This makes it all the more probable that in many of the latter cases a thyroid underfunction which had not had time to become detect-

* At this time the patient's Lugol's solution was being kept in a cork-stoppered bottle. Under these circumstances a reaction takes place between the cork and the solution, as a result of which the cork is slowly destroyed and the solution becomes much paler. This does not occur if the solution is kept in a glass-stoppered bottle.

able clinically was responsible for the low metabolism. Such a theory has particular bearing on Case I (Fig. 1). As stated above, this patient was listed in the study of temporary low metabolism without myxedema (as Case V) on the basis of the data to that date. She had developed a basal metabolism of −25 on iodin shortly after operation, but there was not sufficient clinical evidence to justify a diagnosis of myxedema. On omission of iodin the metabolism rose to standard normal. In the light of the subsequent repeated development of typical myxedema on iodin, with the same depression of the metabolism as just after operation, there is little doubt that the first low rate was also due to a hypothyroidism which did not last long enough to manifest itself upon physical examination.

The fact that iodin may sometimes produce myxedema in patients who have been operated on for exophthalmic goiter, and that there is suggestive evidence that it may sometimes produce it in patients with untreated mild exophthalmic goiter, raises the question of the nature of the action of iodin in that disease.

Until recently it was Plummer's[2,6] contention that in exophthalmic goiter the thyroid gland elaborates two products: (1) An abnormal product, presumably deficiently iodinized thyroxin, which accounts for the peculiar nervous manifestations of the disease which distinguish it from toxic adenoma, and which causes the portion of the increase in basal metabolism that can be controlled by iodin. (2) The normal hormone, which is produced in excess and which causes the portion of the increase in basal metabolism which cannot be controlled by iodin. He has recently modified his theory[7] to the effect that all of the increase in basal metabolism may be due to excess secretion of the normal hormone, and that iodin may affect the secretion of both the normal and abnormal products.*

Haines[1] claims that the case he has reported supports Plummer's hypothesis. In this patient, a woman, aged twenty-eight years, myxedema with a basal metabolism of about −28 could be produced at will by the administration of iodin, following a subtotal thyroidectomy for exophthalmic goiter. The diagnosis of myxedema was based on intolerance to cold, edema of both eyelids, coldness and dryness of the skin and a "facies typically that of myxedema." When iodin was omitted the basal metabolism would rise to about −14, the signs and symptoms of myxedema would disappear, and the patient would complain of nervousness and have a "stare characteristic of exophthalmic goiter." Because of these two findings (that is, nervousness and a stare) the patient was said to be suffering from exophthalmic goiter. A residual exophthalmos was apparently a constant feature and was little affected by the level of the basal metabolism. The author states "If, in this case, the

* A schematic representation of the effect of iodin on the thyrotoxicosis of exophthalmic goiter may be found in a paper by Means, Thompson and Thompson.[8]

phenomena of myxedema could be produced at will by the administration of iodin and by stopping it, these phenomena could be made to disappear and evidence of exophthalmic goiter substituted, we would then have proof of the coincident existence in this patient of both myxedema and exophthalmic goiter. Furthermore, almost incontrovertible evidence would be established in support of Plummer's hypothesis."

It is not clear to us how two conditions can coëxist in the same patient if one disappears when the other is present. This difficulty is apparently partially overcome by later developments. While iodin was continued, sufficient desiccated thyroid was given to maintain a basal metabolism of about −6. The patient then felt better than at any previous period of observation. Iodin was stopped and desiccated thyroid continued in the same dose. The basal metabolic rate rose in fourteen days to +6, the patient "became nervous and warmer, the eyes stared and puffiness of the lids of the type seen in exophthalmic goiter appeared." Inasmuch as relief from symptoms is supposed to have come only from the simultaneous administration of iodin and desiccated thyroid, the author concludes that "there was, then, absolute deficiency of thyroid secretion, and what secretion was present was partially of the character of that produced in exophthalmic goiter."

The evidence of myxedema in this patient appears much more definite than the evidence of exophthalmic goiter. In a patient who already has exophthalmos, a stare might well appear to be present in the alert expression that accompanies a normal level of metabolism, in contrast to the dull listless expression of the myxedematous condition. Slight nervousness may be due to many things.

All of the patients we have reported appeared to be in a healthy state and to present no evidence of exophthalmic goiter when they were not receiving iodin and their basal metabolic rates were at a normal level. In Case I the clinical picture produced by maintaining the basal metabolism at a normal level by the combined administration of iodin and 1½ grains of desiccated thyroid (Armour's) was indistinguishable from that which was produced by causing the metabolism to rise to normal by omitting iodin. Moreover, when the metabolism was raised a little above the normal level by administering 3 to 4½ grains of thyroid daily while iodin was continued, the clinical condition of the patient resembled that of Haines' patient when the basal metabolism was raised to +6 by administering thyroid and omitting iodin. Symptoms of thyroid intoxication from overdosage are not infrequently seen in patients with myxedema, even though the metabolic rate is within standard normal limits.[5]

Thus, so far as we were able to determine clinically, the administration of iodin to our patients caused a diminution in the secretion of what appeared to be the normal thyroid hormone. Inasmuch as iodin may produce this phenomenon, there seems to be no necessity

at present for postulating an abnormal thyroxin to explain the high basal metabolism in exophthalmic goiter.

The actual mechanism by which the reduction in basal metabolism is accomplished is, of course, unknown. Marine's[9] theory that storage of colloid by virtue of the pressure it exerts inhibits cell function and interferes with secretion of the hormone, is a plausible explanation. It does not appear to explain some things however—for example, in a patient with exophthalmic goiter in whom a resting level of basal metabolism has been obtained, as little as 1.5 to 6 mg. of iodin will sometimes cause a drop in basal metabolism within twenty-four hours.[10] In such a short time, even though an increase in colloid may occur, as has been shown by Marine and Rogoff,[11] it seems unlikely that sufficient would be stored on such small doses of iodin to cause "pressure retention." There is the possibility, however, that a sudden slight increase in colloid may be adequate to initiate the change. Although the gland in both Case IV and Case I initially became a little firmer after iodin was administered, at the time of the low metabolisms it was smaller, and at least in Case IV softer, than before iodin was given. In Case IV the first relapse on iodin was associated with some increase in size and hardness.*

While in some of the cases the low basal metabolism can be maintained for long periods (about three months in Cases I and II and about two months in Case III) and perhaps indefinitely on iodin, in others it cannot (Case IV). These variations in the length of time the depression of the metabolic rate can be maintained by iodin appear to be similar to variations that occur at higher levels of metabolism. The first relapse on iodin in Case IV could be attributed to weakening of the iodin solution, but the second such relapse did not have this complicating factor. The condition apparently changed spontaneously from one of mild myxedema to one of mild thyrotoxicosis while iodin was being administered in the same dose. Marine's theory could account for this by assuming that after a time the gland became accustomed to working under increased tension and the effect of iodin wore off. In addition to the objections to this hypothesis enumerated above, it may be said that while it might be adequate to explain the relapse in Case IV, it seems inadequate to explain the remission which followed the relapse during the continuous administration of the same amount of iodin.

It is of interest to inquire whether the action of iodin in causing an underfunction of the thyroid is limited to patients who have or have had definite exophthalmic goiter. At the Mayo Clinic[1] in "several cases . . . presenting the syndrome of exophthalmic goiter and with basal metabolic rates from 0 to ±10" it has been observed

* In Case II the gland was definitely firmer throughout the period of iodin administration, while in Case III no thyroid tissue was palpable at any time after operation.

that the metabolism dropped 5 to 15 points after administration of iodin. No mention is made of myxedema. Strouse and Binswanger[12] could not significantly lower the basal metabolism of several patients with a "symptom complex resembling hyperthyroidism without increased metabolism" by forced iodin feeding. Martin[13] observed a drop in basal metabolism from a normal to a subnormal level in 6 patients with simple goiter "showing symptoms of iodin deficiency." Koehler,[14] referring to a group of patients with "moderate to mild hypothyroidism . . . whose untreated basal metabolic rate falls approximately between 15 to 25 per cent below normal," stated that during administration of iodides many were made worse "both from a standpoint of lowered basal metabolic rate and symptomatology." Segall,[15] Martin,[13] Snell, Ford and Rowntree,[16] Cattell,[17] Strouse and Binswanger[12] and Thompson and Thompson[18] did not observe any change in basal metabolism during the administration of iodin to groups of 1 to 28 normal subjects; and Liebesney[19] got either no change or a rise. Kunde[20] found that "iodin injected intravenously in the form of potassium iodid does not reduce the basal metabolism of normal dogs." Cordonnier[21] did not observe any change in metabolism on administering potassium iodid to normal guinea pigs. Marine, Deutch and Cipra[22] have reported a temporary drop in heat production in 5 of 18 normal rabbits which were fed iodin; and Webster and Chesney[23] in all of 6 normal rabbits in which they tried its effect. Hildebrandt[24] noted that potassium iodide had a depressing effect on metabolism when fed to normal and to thyroidectomized rats.

Thus, a reduction in basal metabolism to a subnormal level has occasionally been produced by administering iodin to patients who have never suffered from exophthalmic goiter and to normal animals. Myxedema, however, has never been produced in them so far as we are aware. Whether or not iodin will cause a lowering of the metabolism more commonly in patients who have a normal metabolism following a subtotal thyroidectomy for exophthalmic goiter than in normal subjects can be determined only by administering it for a sufficient length of time to large series of both types of individuals. It might be expected that an abnormal gland would show this response more commonly than a normal one. Whether the remnant of thyroid gland becomes normal when the basal metabolism returns to normal after a subtotal thyroidectomy for exophthalmic goiter, or whether the disease persists in it, is a matter of conjecture. Another possibility is that the small amount of gland tissue now left at operation in many clinics (2 to 4 gm., on each side) may render the patient more susceptible to myxedema than the larger amount of tissue in normal glands. In Case II iodin was given three times preoperatively and produced a subnormal metabolism (−15) only once. Postoperatively, when there was no palpable thyroid tissue, the depression was more marked and the clinical evidence in favor of

myxedema much more definite. In Case I there was only a small amount of palpable tissue after operation, and in Case III there was none. In Case IV, no surgery was done, and the patient had a fairly large goiter. In this instance the clinical evidence of thyroid underfunction was least satisfactory. Smith, Clute and Strieder[25] think postoperative myxedema has been more common at the Lahey Clinic since they have been doing more extensive thyroidectomies and using iodin postoperatively. A similar opinion is expressed by Graham.[26] The amount of thyroid tissue present thus may be a factor in determining whether or not myxedema will develop when iodin is given. While we have not made a systematic study of the subject, it is of interest that of 54 patients with a normal basal metabolism following a subtotal thyroidectomy, to whom we have given iodin, in 18 a reduction to a subnormal level occurred, but in only 3 definite or even mild myxedema.

The rate with which iodin produced definite myxedema in our cases was very slow (three to four months in Case I and in Case II after operation), yet was about the same as the rate at which a comparable degree of hypothyroidism recurs following a single intravenous injection of 10 mg. of thyroxin into a patient with typical spontaneous myxedema.[27] Moreover, the rate with which iodin reduces the high basal metabolism of exophthalmic goiter from a level of +40 to normal (approximately seven to ten days) is about the same as the rate with which the basal metabolism drops from a similar high level to normal when thyroid is omitted in an initially nontoxic patient who has received an overdosage. (See Figs. 6 and 3 in articles by Segall and Means[28] and Starr, Segall and Means[29] respectively, part of the data being on the patient of Aub and Stern.[30]) These similarities in themselves suggest that it is a normal and not an abnormal hormone, the secretion of which is reduced by iodin.

While the speed with which iodin causes a normal basal metabolic rate of a postoperative case of exophthalmic goiter to drop to a low level in association with the development of myxedema is usually much less than that with which it causes a reduction in the high metabolism of a typical untreated case of the disease, there is no good reason to suppose that the mechanism in the two is different. There would appear to be merely an upward shift in the scale of metabolism throughout. This is upheld by the data on Case IV and Case II. In Case IV at one time the basal metabolism fell from +32 to −20 (52 points) on iodin; and in Case II before operation it fell from +26 to −15 (41 points). That portion of the drop which was from the normal to the subnormal level was evidently just a continuation of, and of the same nature as that portion of the drop which was from the high to the normal level.

The contrast in the frequency and generally in the speed with which iodin depresses the basal metabolism in exophthalmic goiter

when starting at a high level as compared with the relative rarity and slowness with which it depresses it when starting at a normal level after operation, is probably just an example of the general rule that in most biologic reactions it is more difficult to initiate a change from a normal to an abnormal state than a change from an abnormal to a normal one. An analogy lies in the action of thyroxin. In a patient with myxedema, the magnitude and duration of the effect of 10 mg. is much less if it is injected when the metabolism is maintained at a normal level by desiccated thyroid than if it is injected when the metabolism is low.[27]

From the standpoint of routine clinical treatment, any patient with exophthalmic goiter who develops myxedema during the postoperative administration of iodin need not be treated with desiccated thyroid unless the myxedema persists when iodin medication is stopped.

Summary. The data presented in this and in a previous paper,[3] on the rôle of iodin in the production of low basal metabolism following exophthalmic goiter, may be summarized here.

During the administration of iodin to a patient whose basal metabolism is standard normal following a subtotal thyroidectomy for exophthalmic goiter, any one of the following effects may be noted:

1. No response—the most common result.
2. Depression of the basal metabolism to a subnormal level without any accompanying clinical evidence of underfunction of the thyroid gland.
3. Depression of the basal metabolism to a subnormal level, in association with the development of myxedema, as exemplified by cases described in this article.

The latter two types of response are occasionally seen in mild untreated cases of exophthalmic goiter.

The third type of response is rare, and in this Clinic has been noted in only 3 cases following operation and in only 2 preceding operation.

In the patients reported in this paper, 1.5 to 4.5 months elapsed from the time iodin was started until the basal metabolism dropped from a standard normal level to its lowest point and myxedema developed.

The myxedema could be made to disappear either by omitting iodin or by continuing iodin and giving thyroid in addition. Both procedures produced the same clinical picture.

The development of myxedema during iodin administration is not confined to the immediate postoperative period, but may occur years after operation.

The patients who developed myxedema following operation appeared to be in a healthy state when their basal metabolism was normal and they were not receiving iodin.

Conclusions. So far as can be determined clinically, the myxedema which occasionally develops during the administration of iodin to patients who have a normal basal metabolic rate following a subtotal thyroidectomy for exophthalmic goiter, is due to an inhibition of the secretion of the normal thyroid hormone.

This suggests that iodin may cause a reduction in the high basal metabolism of exophthalmic goiter in the same manner.

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PROGRESSIVE LIPODYSTROPHY APPEARING AT MENOPAUSE.

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Progressive lipodystrophy as a clinical entity is not new to medical literature, as about 84 cases have been reported since 1906. The clinical variations in the particular case which we have observed offer an opportunity for some interesting speculation, particularly as to the time and mode of onset and the possible relationship of etiology to certain endocrine changes.

Barraquer,[2,34] of Barcelona, in 1906, published the first recognized account of a case of lipodystrophy, although a case had probably been previously observed by Morgagni[39] and another by Osler (1895). The description of a typical case as observed by the earlier writers reveals the fact that the disease is principally one of signs rather than symptoms. It begins usually in the first and second decade and is characterized by a striking loss of subcutaneous fat over the upper part of the body down to about the level of the umbilicus, while the fat below that level is either normally retained or markedly increased. In 1907 Campbell[2] showed before the Clinical Society of London a true case in a woman, aged twenty-two years, and in 1909 Pic and Gardere[2] reported a case which was typical in all respects except for exaggerated tendon reflexes. The term "progressive lipodystrophy" was used first by Simons[2] in 1911.

Five rather complete reviews have appeared in the literature, the most extensive being that of Reuben, Zamkin and Fox,[24] which was published in 1924 and contained a résumé of 60 cases. Ziegler[43] recently published the largest series of cases observed by a single individual, and in so doing he made some interesting observations on the sugar metabolism and mental state in this disease. Christiansen[6] claims to have observed in the course of ten years 15 cases, but to our knowledge has reported but 4 of these.

Practically nothing is known of the etiology of this disease, although many theories have been advanced by various writers. The disease is not confined to any particular race, although several writers have suggested its predominance in Hebrews. A review of the literature does not confirm the opinion. No one lays any stress on heredity as having any significance in the etiology. However, our patient's family history would strongly suggest the possibility of an hereditary disturbance of fat metabolism. Her mother weighed over 200 pounds, and a brother, a sister, a half sister and a half brother are all extremely obese and have been so since childhood. Two of her sons and a daughter are overweight. The daughter, who was unusually fat as a child, has recently been married and is gradually becoming still more obese. Zalla,[40] Marañon and Soler[20] suggest that "lipodystrophy is nothing more than an extremely accentuated form of distribution of adipose tissue and, therefore, not uncommon. In consequence, there is a whole series of gradations of intermediate forms between the accentuated cases and the normal state." Excessive fat of the buttocks, "steatopygia," is seen as a normal development in the female of certain African races. Gesell[11] has recently reported 2 cases of hemihypertrophy in children and "interprets the condition to be an atypical or a paradoxical form of twinning." Considering a disturbance in fat metabolism as the possible etiology of the disease, Mirallié and Fortineau[22] tried high-caloric diets with no gain of fat in the atrophic areas. Sprunt[30] was more successful with the same type of diet, but, in addition, he used pituitary gland and sodium cacodylate.

Boissonnas[2] expressed the unique theory that the atrophy above the waist line was pathologic while the hypertrophy below represented an attempt at compensation present in the whole body but effective only in that area. There is certainly some alteration in fat metabolism in cases of "intestinal lipodystrophy" as reported by Whipple,[37] Blumgart and Tucker.[32]

Whipple[37] applied the term to an unusual case he reported in 1907, which was characterized by a progressive loss of weight and strength, indefinite abdominal and arthritic pains, and associated with frequent stools containing large quantities of neutral fats and fatty acids. Only 1 of the 5 cases reported has come to necropsy. The pathologic findings were enlarged intestinal villi, lymph spaces filled with large masses of neutral fats and fatty acids, and an

infiltration of the interglandular tissue by large mononuclear and polynuclear giant cells.

Infection or the toxic effect of an infection producing organic changes in the brain has been proposed as a theory to explain the remote changes found in the distribution of fat elsewhere in the body. As will be mentioned later, the neuropathology concerning this particular disease is still far from being definitely established. It might be mentioned that Wartenberg[33] has suggested the possibility of an "encephalitic" infection or toxin involving an area in the region of the brain stem, mesencephalon or third ventricle.

The endocrines offer a field for interesting speculation in this disease, as with many other metabolic disturbances. In 3 of Ziegler's cases, the metabolic rate was high, and in 1 of these cases there were recurring attacks of exophthalmic goiter. A series of 7 cases showing disturbances of the thyroid was reported by Maranon and Soler.[20] Many writers, including Klein,[12,28] Christiansen[5] and Marburg,[21] have believed the syndrome to be a combination of endocrine and neurotrophic disturbances. One of Klein's patients responded to treatment by pituitary extract. Sprunt[30] reported similar results, but, in addition, gave a high-caloric diet. A question of involvement of the pineal gland was raised by Kelin,[7,23] who suggested that excessive localized atrophy of the gland at its involution (at age of six, which is age of usual onset of lipodystrophy) produces irregular function of the gland and consequent disappearance of fat in certain areas, the increase in fat below the waist being a secondary sexual characteristic of puberty. But, as Watson and Ritchie point out, the pineal syndrome of excessive height, general adiposity, hypertrichosis, somnolence and sexual precocity is not seen in lipodystrophy.

To support the theory of pituitary disturbance in this disease, one naturally associates the well-known syndromes, such as Frölich's and Lorain-Levi and also the numerous metabolic disturbances which are due to pituitary dystrophies. In reviewing our cases of pituitary disease, we selected one, a Lorain-Levi type, which we believed showed some relationship to the case in question. A brief description will illustrate our point.

Case Abstract of Lorain-Levi Syndrome. The patient was sent to the clinic because of amenorrhea. Family history was entirely negative. Her past health was good, except that she had had the usual exanthems of childhood. Recently she had an epiphyseal separation of the right femur at its proximal end. Roentgenograms at that time showed all epiphyseal lines still open in hands and feet. On examination, we found a fairly well-nourished girl, aged twenty years, lacking all secondary sexual characteristics and having infantile pelvic organs. The lack of adipose tissue and bony development gave her the appearance of a slender preadolescent male (Fig. 1). Roentgen ray findings confirmed clinic suspicions as the films of the head showed a marked enlargement of the sella turcica (Fig. 3) with several calcified areas and the skull was somewhat thin. There was a moderate widening of the suture lines, suggesting an increased intracranial pressure.

We have, therefore, a case of the Lorain-Levi type (preadolescent hypoactivity of the anterior lobe) of pituitary disturbance giving us much the same picture that we see in the upper part of the body in a case of progressive lipodystrophy.

Frazier,[45] in his recent review of 15 cases of pituitary cachexia (Simmonds' disease) has shown that there may be an extreme emaciation of the trunk and extremities. The emaciation, or total lack of adipose tissue, in the trunk and upper extremities in pituitary cachexia, Lorain-Levi syndrome, and progressive lipodystrophy is decidedly similar, so the idea that there may be a pituitary disturbance in the latter disease is not so remote. Of course, the entire question of the causal factor in lipodystrophy is in the realm of theory and no one knows which factor may be of the most importance.

Neurotrophic disturbances have been mentioned more frequently in discussions as to etiology than any other factor. One can readily surmise that the discussion of the trophic nerves or neurotrophic centers is still in the field of hypothetical consideration, and that it leads one into much speculation concerning the association of neurotrophic and endocrine factors as a combined cause of the disease. Trophoneurosis, perhaps due to abnormal innervation, has been suggested by Rominger.[27]

The segmental arrangement of the disease in some cases has pointed toward the basal ganglia as being the site of the involvement. The disturbance in fat distribution in the lower part of the body closely resembles, though highly exaggerated in some cases, that of women at the menopause, and the possibility is not so remote that this disturbance may be due to an endocrine dystrophy, while that of the upper part of the body is due to a neurotrophic disturbance. Klein[12,28,43] believes that all the signs in this disease are due to disturbances of the glands of internal secretion and of the sympathetic nervous system and that a subthalmic vegetative center plays the most important rôle. He thinks the center must be regarded as "localizatory differentiated," because only the upper part of the body becomes emaciated. The accumulation of fat in the lower part remains unexplained. Since lipodystrophy usually affects females during puberty, Klein[12] believes it is connected with the maturing of the ovaries. Wolff and Ehrenclou[38] also consider the disturbance as possibly due to a general imbalance caused by pathologic change in trophic centers at higher levels.

The pathologic findings from biopsies performed by Simons,[2] Christiansen,[6] Feer[10] and Smith[29] were uniformly the same. The epidermis and dermis were found to be normal; the one histologic change observed in all cases was the practically complete absence of fat in the subcutaneous tissue. No microscopic changes were found in underlying muscles. Necropsies are also reported by Husler, Sarbo, and Weber and Gunewardene.[35] The latter observ-

ers report a case of a girl, aged thirteen years, who died of pyemia following a left mastoid operation. Microscopic examination of glands, one ovary, pituitary and both suprarenals showed no unusual findings. There was an abnormal amount of colloid in the acini of the thyroid gland, and there was more than the normal amount of interstitial tissue present. Sections from various parts of the gland suggest that there was a moderate degree of oversecretion of colloid which was associated with a slight fibrosis and actual diminution in the size of the gland. Histologically, there was no fatty tissue present in the scalp or upper abdominal wall. Consistent pathologic findings which would have any bearing whatsoever on the etiology have not been found. For instance, Sarbo reports a case showing a lesion in the corpus striatum, while Zalla reports another of a pituitary cyst. Sprunt shows one case having a persistent thymus and still another with atrophy of the thymus. A detailed pathologic report of brain findings is contained in the article by Otto Marburg, but the value of his observations is depreciated by the fact that the patient died of a purulent septicemia.

The symptomatology in this disease is indeed meager, since practically the only complaint is weakness. Ziegler,[42] in his recent review of 82 cases, gives particular attention to the "neuropsychiatric aspects of lipodystrophic disturbances." He states that in 15 cases there was a marked self-consciousness; in 17 cases the family or friends were worried about the patient's health; in 8 cases nervous and mental symptoms were rather prominent; in 43 cases no abnormality of behavior was noted. Our patient has never shown any neuropsychiatric symptoms.

Treatment. No form of method of treatment has as yet been found to be of particular value. Of the glandular preparations, whole pituitary has been beneficial to some patients complaining of weakness. Ziegler[43] has reported some success with ovarian extract. Two cases, both women, reported by Boston,[3] in 1923, showed some improvement under treatment. The treatment in each case consisted of three capsules daily containing small doses of cerebrin, strychnin sulphate, parathyroid, whole pituitary and potassium citrate. Case 1, a woman, aged thirty-one years, took the capsules daily for fourteen months and gained 17 pounds. Case 2, a girl, aged sixteen years, followed treatment for a shorter period and gained 7 pounds. The experience of Mirallié and Fortineau[22] with rest and high-caloric diets has not been encouraging. Sprunt,[30] however, reports success in one case with rest and forced feeding. This form of treatment should be tried. Protracted administration of insulin was tried by Rominger with negative results. The body weight did not increase, there being only a further accumulation of fat in the lower parts of the body. No writer has ever been able to cause any change in the facial condition other than by subcutaneous injections of paraffin, which have been of questionable value.

FIG. 1. — Case I. Girl, aged twenty years, showing lack of adipose tissue, bony development and secondary sexual characteristics.

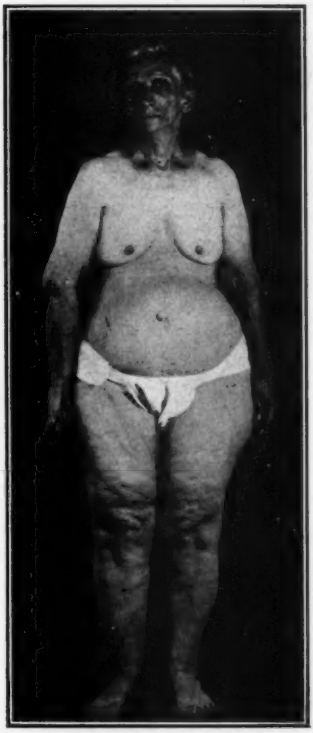

FIG. 2.—Case II. Fat pad shown on right elbow. Note lack of fat in face and chest, with an increase below the waist.

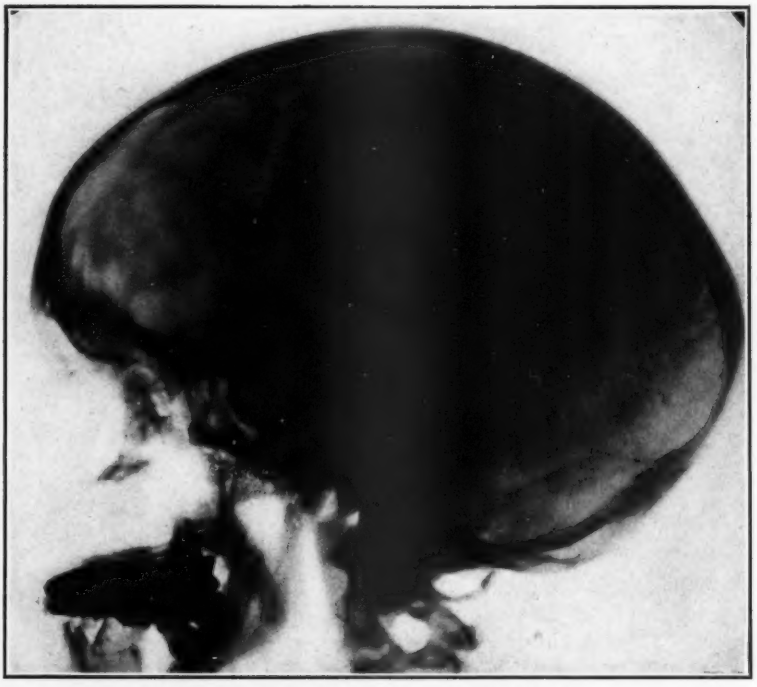

FIG. 3.—Case I. Note enlarged sella with calcified areas.

FIG. 4. — Case II. Appearance of patient at the age of twenty-five years.

FIG. 5. — Case II. Cadaveric expression due to loss of subcutaneous tissue.

Case Report of Lipodystrophy. Mrs. M. H., aged sixty-five years, housewife, came into the clinic complaining of a loss of fat in both sides of the face and an increase in fat about the hips and thighs.

Family History. The patient has a brother, sister, half brother and half sister who are obese, and have been so since childhood. Her maternal aunts and uncles have all weighed over 200 pounds.

Past History. Other than the usual exanthems of childhood, she had typhoid fever at the age of seven years. Asthma has been disturbing to her since the age of twenty-five years. It is worse in damp weather.

Menstrual History. Her periods began at the age of eleven years, and they ceased at thirty-nine years; otherwise they were normal.

Marital History. The patient was married at twenty-five years (Fig. 4). She states that at that time she had small breasts. She gave birth to five children, four sons and one daughter. The first and fourth sons weigh over 180 pounds. The third son has goiter and the second son has idiopathic epilepsy, which began at twenty-four years. The latter, whom we shall mention later, has total blood lipoids of 333 mg. per 100 cc. (normal, 200 mg. per 100 cc.) and a cholesterolemia of 221 mg. per 100 cc. (normal, 140 to 170 mg. per 100 cc.).

Present Illness. After the age of forty years (menopause) she began to rapidly take on the fat in the arms, lower abdomen and legs. The increase of tissue below the umbilicus and the decrease above made it impossible for her to use a shopmade dress. In the spring of 1928 (age of sixty-four years) she reached her greatest weight of 203 pounds, due to the increase in fat about the hips and thighs, while the face took on a cadaveric expression (Fig. 5). At about the same time she noted a gradual decrease in the fat of the arms except for fad pads which remained at the elbows (Fig. 2).

Examination. General: The patient's weight is 176 pounds, and she is 63½ inches tall. She appears about her actual age. Her hair is gray. The face shows the typical loss of subcutaneous fat. The skin of her hands is dry and shiny; that of her arms, particularly the upper arms, is flabby. The skin over the upper arms can be raised several centimeters; definite fat pads can be seen over the elbows. The thorax and upper abdomen, down to the umbilicus, are rather thin. The breasts are flattened and contain little fat or glandular tissue.

Vision: Right, 6/30−; left, 6/30−. Pupillary reflexes are normal. Arcus senilis is present in both eyes. Fields are normal, and fundi are negative with the exception of marked sclerosis of the vessels.

Oral cavity: There are complete upper and lower dentures. The throat shows chronic injection over both anterior pillars. The tonsils show moderate fibrosis with few crypts and follicles. There is no free pus, but a mild chronic injection over the pharynx. Few enlarged cervical glands—tonsillar glands—are palpable. Aside from a small shelf along both floors, the nose is negative. The ears are negative, and the sinuses, clear.

Heart: Rate is 64. Rate and rhythm are regular. Sounds are normal and there are no murmurs. Blood pressure is 170 systolic and 90 diastolic, No cardiac enlargement is present. The lungs are normal to inspection, palpation, percussion and auscultation. Liver and spleen are not palpable. No tumor masses nor tender areas are found in the abdomen.

Neurologic examination: Her gait and station are normal with eyes opened or closed. She has an interesting, unusual padding of fat over the elbows. There are no tremors of the hands on extension. She has a radial deviation of the terminal joint of both forefingers. There is no intention tremor, no ataxia, no astereognosis, no adiadokokinesis. The patient states that when she was younger she had a marked laxity of the elbow joints. This is still present to a certain extent.

Cranial nerves: She has no facial paralysis. There is apparently considerable atrophy of the lower facial group of muscles, but there is no loss of motor ability. She moves the jaws, closes the eyes normally. The palate moves normally. The tongue is quite smooth in appearance. The extraocular movements are normal. The consensual reflex is normal. There is no nystagmus.

The deep reflexes are normal. There is no Babinski and no clonus. She has varicose veins in the right leg. Her toe nails are unusually dry and hard. There is a tendency toward marked convexity of the nails, especially of the great toe on each foot.

Sensation: Vibration, pain, light touch, motion and position, and deep pressure are all normal.

Laboratory Findings. These include: Urine: Light yellow, clear; negative for albumin, glucose, indican and casts; few red blood cells; many white blood cells and vaginal epithelial cells. Blood count: Hemoglobin, 85 per cent; red blood cells, 3,650,000; white blood cells, 4650. Differential count: Lymphocytes, small, 43; transitionals (endotheliocytes), 4; polymorphonuclears (neutrophils), 51; eosinophils, 0; basophils, 2. The Kahn test was negative. Total lipoids: 298 mg. per 100 cc. (normal, 200 mg. per 100 cc.). Cholesterol: 229 mg. per 100 cc. (normal, 140 to 170 mg. per 100 cc.).

Roentgen-ray Findings. Films of the head are negative. The sella turcica is of normal size and without bone erosion.

Comment. Although our case has contributed several interesting points, it has added nothing toward the solution of the etiology of the disease. Examination of the photographs will convince the reader that the case presented is a typical progressive lipodystrophy, closely resembling Case 2 of Ziegler's recent series, with the exception that our case presents fat pads at the elbows which have the appearance and feeling of small lipomas. Bavonneix cited a case in 1923 with similar pads.

Our case is unusual in that the disease did not make its appearance until after the menopause, and perhaps some speculation could be offered as to the question of this being an ovarian or an ovarian-pituitary dystrophy. She always had small breasts, and never took on weight above the umbilicus except in the arms. The loss of fat above the level of the umbilicus suggests the possible association of this disease with pituitary cachexia and also with Lorain-Levi type of pituitary dystrophy.

Our patient has had asthma which dates from the time of marriage and we know of no other case reported to have a like complication. Perhaps the most common complications reported are diabetes mellitus and hyperthyroidism. Nervous and mental symptoms have never disturbed her, and she has had none of the usual signs of weakness and fatigue.

The few blood chemistry findings reported by other writers show no abnormalities. Feer even tried to produce a lipemia by administering 200 gm. of 20 per cent cream by mouth, but failed. Our case shows both a high-cholesterol and high-total lipoid blood content, as is also true of her son who has epilepsy. Whether or not

these chemical findings are of any significance, we are at present unable to say. Her family history suggests the possibility of an hereditary disturbance in fat metabolism.

Summary. 1. A case of progressive lipodystrophy appearing after the menopause is presented.

2. A case of Lorain-Levi type of pituitary dystrophy is cited to show a possible association of endocrinopathy and progressive lipodystrophy.

3. A high cholesterol and total lipoid content in the blood of both the patient and her son suggests the possibility of a familial disturbance in fat metabolism. However, we would hesitate to say it has any significance as regards the etiology of the disease.

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PROGRESSIVE LIPODYSTROPHY OF THE LOWER EXTREMITIES.

Report of a Case.

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In view of the full discussion of this rather rare and interesting condition by Currier and Davis in this issue, I am briefly reporting this case because of two features unusual in this group of patients. The lipodystrophy appears at or about the menopause, and shows a reversed distribution of the fatty changes. Sprunt, in describing the condition, says that "It is characterized by a remarkably complete disappearance of the subcutaneous fat of the face, of the neck and usually of the arms and upper portion of the trunk. This emaciation begins, as a rule, in childhood, first involves the face and then the lower parts progressively from above downward. Simultaneously or beginning a few years later there is an excessive deposit of subcutaneous fat on the lower portion of the trunk and on the legs, which may be in grotesque contrast with the emaciation above the waist."

Case Report. Mrs. M. O., aged fifty-five years, first consulted me in January, 1930, complaining of pain under and between the shoulders and loss of weight. She reported that she had diabetes and high blood pressure.

Family History. Native, white, American stock. Mother and two uncles died of Bright's disease. Several brothers and sisters are quite well and of average size and weight. There is no record of a similar condition in her family.

Past History. Since childhood, no illnesses except tonsillitis and influenza in 1928. Tonsils were removed in 1928.

Marital History. The patient has been married three times. The first when she was twenty years of age. There was one child and after three years her husband died of tuberculosis. The second marriage resulted in the birth of four healthy children. There were other pregnancies, twice with twins, all of whom were lost and once a premature birth which died. Her third marriage was only five years ago. The menopause was complete at fifty years.

Present Illness. The patient's legs began to lose all superficial fat and their former shape about three years ago. Two years ago this loss seemed complete, and since that time there has been no further change in their appearance. The patient had been through a rather exhausting nervous strain just before this. Immediately after the menopause she lost her father with pneumonia. Her mother was a semi-invalid and her care was trying. It was during this time that she first noticed the "wasting away" of her legs and she worried a great deal about their appearance.

Following an attack of influenza in 1928 she has suffered with pains between the shoulders, which she describes as feeling like a great many sharp knives sticking under her shoulders. There is also numbness in both arms at times. Two years ago she consulted a physician who found a rather high blood pressure and sugar in several specimens of urine. She was given diet instructions and advised to have her tonsils removed. After tonsillectomy the pains and numbness were better, and pains that had been present in the lower extremities disappeared. She states positively that at this time there was absolutely no fat present over the lower extremities.

Physical Examination. The patient's lower body presents a striking contrast to the upper portion. The hips, thighs and legs are so slender that they might have well belonged to another person. (Note photograph.) The arms, neck, chest, abdomen and breasts are well covered with subcutaneous fat. From the level of the waist down there is absolutely no palpable subcutaneous fat. The contour of the muscles of the thigh and leg are clearly discernible, the legs appearing quite masculine. The hips and gluteal regions are remarkably thin and flat when compared to the abdomen and shoulders above. The loss of fat is bilaterally symmetrical. It is just the reverse of the usual distribution in the cases of lipodystrophy heretofore reported.

The essential findings on physical examination were important. There were no demonstrable neurologic changes. All deep and superficial reflexes were present normally on both sides in the upper and lower extremities. There were no Romberg or Babinski signs, no clonus, no sensory changes to touch, pain or temperature at any point. There was no muscle weakness, no interference with locomotion and, in short, nothing to indicate an organic neurologic basis for the condition, except the symmetrical deformity and the abrupt level of change in the distribution of subcutaneous fat.

The patient's weight is 138 pounds; height, 64 inches. Her average weight had been until this last year, 155 pounds. The loss of 15 pounds she attributed to diet efforts to control glycosuria.

Vision shows slight error, readily corrected. Pupils equal, active to light and in accommodation. Ophthalmoscopic inspection shows normal fundi except for slight sclerosis. Diseased tonsils and teeth had been removed. The thyroid was not enlarged and there were no evidences of

disturbed thyroid secretion. No enlarged glands in the cervical triangles, either axilla, about the elbows or in either groin. The breasts are large, flabby and pendulous.

Mrs. M. O., lipodystrophy of lower extremities.

The heart is slightly enlarged to the left. No murmurs, no accentuations, regular rhythm, rate 86 to 90. The radials and brachials are palpable and slightly thickened. Fluoroscopic examination of the chest and heart shows a slight increase in heart size and some widening of the aortic arch. The lung fields are clear. The blood pressure is 165 systolic and 90 diastolic.

The abdomen is relaxed; no masses; no areas of soreness. Vaginal examination negative, except for some relaxation of the outlet and an old cervical tear. Rectal examination shows small external hemorrhoids.

Laboratory Findings. Urines (three specimens) all showed traces of albumin, sugar in fairly large amounts, no acetone and microscopically only an occasional hyaline cast. Hemoglobin, 85 per cent (Dare); red blood cells, 4,350,000; white blood cells, 6750. Differential count: Polymorphonuclears, 54 per cent; lymphocytes, 35 per cent; mononuclears, 5 per cent; eosinophils, 6 per cent. No plasmodia found. Blood Wassermann test negative. Kahn negative. Spinal Wassermann test negative. Blood sugar: Fasting, 181 mg. per cent; two hours p.c., 285 mg. per cent. Feces: No ova or parasites found. Basal metabolic rate, −7.

Radiograph of the sella turcica: Normal in size and contour.

Summary. A case of progressive lipodystrophy with two unusual features is reported.

1. The lipodystrophy involves the lower extremities rather than the upper body as heretofore reported cases have done.

2. The lipodystrophy first appeared in this case after the menopause.

NONDIABETIC GLYCOSURIAS.*†

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In a series of previous communications[1,2,3,4,5,6] one of us has reported the results of studies on various aspects of the metabolism of galactose in health and disease and described the technique of a tolerance test based upon its use. The present report deals with a study of patients who have demonstrated a spontaneous glycosuria without direct evidence of diabetes and presenting a variety of disease conditions not intrinsically associated with the pancreas. Before discussing the methods adopted and the results obtained, a few words of definition are necessary.

The term "diabetes" is gradually being delimited to that disturbance of the carbohydrate metabolism produced by a deficiency of insulin, the product of the endocrin activity of the islands of Langerhans. Glycosuria is but one evidence of the condition and one not wholly indicative, as both the treated diabetic can be rendered sugar free and various artificial agents can produce it. Hyperglycemic blood-sugar levels offer much more certain evidence of the presence of the disease, yet even here the occasional observation of an insulin-resistant patient raises the question of a possible second mechanism. The antagonistic action to insulin of the extract of the posterior lobe of the pituitary has been demonstrated by several,[7] but in a patient studied by the author and recently reported by a colleague,[8] an insulin-resistant hyperglycemia developed after the surgical removal of the posterior hypophysis, the latter fact being verified at autopsy. Further, the enormously increased tolerance for carbohydrate exhibited by the severe case of pituitary failure with a completely normal blood sugar offers yet another stumbling block to a theory of causation that involves insulin activity alone. The term diabetes will be confined in this paper to that disease entity which is traceable directly to a condition of lowered endocrin function of the islands of Langerhans. The warrant for such position is supported by ample authority.[9] That insulin *qua* insulin may be involved in the mechanism of some of the other glycosurias is conceded. Equally, true pancreatic diabetes may and does coëxist with other endocrin and nonendocrin

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conditions which in themselves are capable of causing glycosuria. The terms "renal" glycosuria, "benign" glycosuria and others have been applied to those conditions in which there is a common finding of sugar in the urine but no other evidence of functional or organic disease of the pancreas. In these states the common end result is more than compensated by a variety of clinical and laboratory evidence wholly at variance with those features produced by known pancreatic disease.

The subject is a large one, the literature, both polemical and recording, vast and no attempt may be made here to do more than offer certain objective evidences which bear on the problem. The title of this paper defines a position only and is hoped to be sufficiently broad to be inclusive. The present statement is frankly preliminary in character. The questions involved are of major import and the whole field characterized by many contradictory opinions and interpretations, each of which, however, is able to marshal an impressive array of evidence felt by some to be supporting. It is intended that the facts here recorded may make some contribution to the ultimate resolution of certain of the problems involved. No attempt is made to review the extensive literature, the few citations given being expository to the text and included solely for that reason. This explains what would otherwise be an overfrequent reference to the senior author's publications.

This study draws its material from a consecutive series of nearly 2000 patients referred for diagnostic investigation. While all presented initially some evidence of possible endocrin disorder, both the absence of glandular disease and an underlying nonendocrin disturbance was demonstrated in more than one-third of the series. The methods of investigation have been described in some detail elsewhere.[10] Briefly, it may be stated that each patient received an intensive clinical and laboratory study, and the facts thus elicited were interpreted in terms based upon the previous study both of a long series of normal controls and a similar group of established endocrinopathies. The various facts were interpreted in terms of ductless glandular disease only after a possible causative nonendocrin condition had been eliminated by test and observation. Finally, the differentiation of the several glandular conditions from one another depended on a similar analysis of the evidence[11] and comparison and contrast with established criteria.

Age. In the majority of cases the age at which the patient is referred for diagnostic study is not that of the onset of the condition. Further, consideration of the latter is not more helpful, as patients will frequently date the beginning of a condition from some outstanding event in their medical history which actually has nothing to do with the real difficulty. In series of sufficient length these factors should be compensatory and so the relative figures assume meaning. Review of the age groupings for the entire series and

for that portion showing glycosuria, demonstrates no significant differences and thus eliminates an age element.

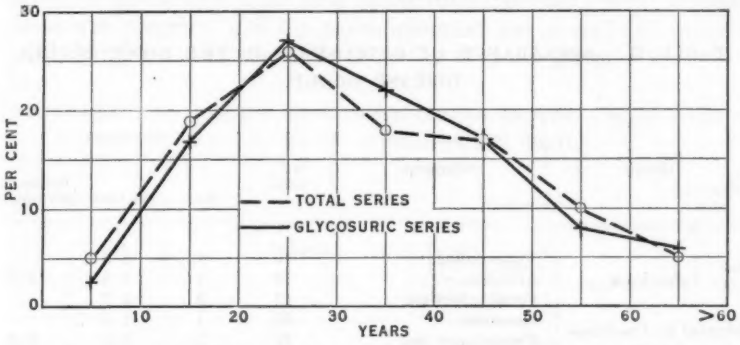

CHART I.—Comparison of age incidence in cases with glycosuria and those of the complete series from which the former are drawn.

Sex. The possibility of a sex influence can be resolved in the same way. The data are given in Table I.

TABLE I.—SEX PROPORTION IN CASES WITH GLYCOSURIA.

Group.	Number, total.	Females.		Incidence in complete series, per cent.
		No.	Per cent.	
Nonendocrin	80	43	54	63
Pituitary	103	63	62	60
Thyroid	46	31	67	73
Gonad	47	47	100	95
Adrenal	6	4	67	67
Pluriglandular	4	4	100	97

The correlations in all but the nonendocrin and thyroid groups give no support to a possibility of sex influence. The gonad figures are but one more evidence of the absence of any testicular influence upon carbohydrate metabolism[12] in adult years at least. In the nonendocrin group a possible sex element is apparent, and this suggestion receives some support from the fact, to be noted later, that many of the thyroid cases show nonendocrin complications which are themselves associated with glycosuria. If the group be taken as a whole the differences are not striking (2.5 per cent), and a male influence, if present, is not of large magnitude nor is it operative in the endocrin group.

As the present survey is designed solely to trace possible influences in the production of glycosuria, the group presenting evidences of disease of a nonendocrin character first claims attention. Any of these conditions may occur as complications in the endocrin group, while naturally, on the present basis of classification, the converse cannot obtain. Certain essential data from the former series have been collected into tabular form. The etiologic designation of each

case is based upon that condition presented by the patient which was considered to be of primary importance. Secondary complications will be considered later.

TABLE II.—APPEARANCE OF GLYCOSURIA IN THE NONENDOCRIN DISEASE GROUP.

Group.	Subgroup.	No., total.	Glycosuria.		
			No.	Per cent.	Group, per cent.
Infections	Tuberculosis	40	1	2.5	3.4
	Arthritis	36	1	2.8	
	Focal infection	43	2	4.7	
Mental and nervous diseases	Neuroses	52	1	1.9	5.5
	Psychoneuroses	40	2	5.0	
	Psychoses	18	3	16.7	
Disorders of nervous system	Central lesions	64	18	28.1	18.3
	Epilepsy	24	1	4.2	
	Parkinsonian syndrome	17	2	11.8	
	Mental retard.	15	1	6.7	
Metabolism	Malnutrition	26	2	7.7	7.7
Disorders of cardiovascular system	Cardiac	47	4	8.5	5.3
	Renal	43	2	4.7	
	Cardiorenal	43	1	2.3	
Blood diseases	Primary anemia	11	2	18.2	19.0
	Leukemia	10	2	20.0	
Tumors	Neoplasm, malignant	10	4	40.0	18.4
	Neoplasm, benign	6	1	16.7	
	Nontoxic goiter	22	2	9.1	
Ear diseases	....	68	2	2.9	2.9
Asthma	....	15	1	6.7	6.7
Diseases of liver	....	62	14	23.0	23.0
Syphilis	....	40	10	25.0	25.0
Normals	....	33	1	3.0	3.0
Totals	....	785	80	..	10.2

Ten per cent of a group of nearly 800 patients presenting a variety of conditions demonstrated sugar in the urine. A further inspection shows, however, that significant relative occurrence is confined to but a few of the several etiologic groups.

The psychoses, lesions of the central nervous system with the Parkinsonian cases which really belong in this category, the blood diseases, malignant neoplasms, diseases of the liver and syphilis, account for nearly 70 per cent of the total number, while the scatter of the remainder lacks any clear-cut definition. Since these several conditions appear with suggestive frequency, their occurrence as complications is pertinent in those cases initially listed under another etiologic group. These data are collected in the next table. The blood diseases and malignant neoplasms are omitted as they did not present as complications in this series.

The case with asthma in Table II is omitted as the patient was under heavy suprarenin medication, a fact potentially introducing another mechanism than that under investigation. The "normal" case was pregnant and the psychoneuroses are as suitably regarded as belonging to the psychotic as to the neurotic group.

TABLE III.—EFFECT OF COMPLICATIONS IN THE CASES WITH GLYCOSURIA IN NONENDOCRIN GROUP.

Group.	Subgroup.	Complicated.				Uncomplicated.	
		Total with glycosuria.	Central nervous system.	Liver.	Lues.	No.	Per cent.
Infections	Tuberculosis	1	0	0	0	1	2.5
	Arthritis	1	0	0	1	0	0
	Focal infection	2	0	0	0	2	4.7
Mental and nervous diseases	Neuroses	1	0	1	0	0	0
	Psychoses	3	0	0	0	3	16.7
Disorders of nervous system	Central lesions	18	..	0	0	18	28.1
	Epilepsy	1	..	0	0	1	4.2
	Parkinsonian syndr.	2	..	0	0	2	11.8
	Mental retardation	1	..	0	0	1	6.7
Metabolism	Malnutrition	2	0	1	0	1	3.8
Disorders of cardiovascular system	Cardiac	4	3	0	0	1	2.1
	Renal	2	0	1	1	0	0
	Cardiorenal	1	1	0	0	0	0
Blood diseases	Primary anemia	2	0	0	0	2	18.2
	Leukemia	2	0	0	0	2	20.0
Tumors	Neoplasm, malignant	4	0	0	0	4	40.0
	Neoplasm, benign	1	0	1	0	0	0
	Nontoxic goiter	2	0	1	0	1	4.5
Ear disease	....	2	0	0	0	2	2.9
Liver diseases	....	14	0	..	0	14	23.0
Syphilis	....	10	0	0	..	10	25.0

That glycosuria is associated with a variety of endocrin conditions outside of the prototype produced by pancreatic hypofunction has long been recognized and frequently recorded. A certain confusion has arisen at times through failure to recognize the possibility of changing function levels in the same disease state, although Cushing[13] a number of years ago recorded this phenomenon with the pituitary in acromegaly.

The present endocrin series is no exception to this general rule. Following the procedure adopted for the nonendocrin material, the data have been collected in tabular form. The dysfunctional pituitary group is composed of those cases in which diagnostic study has demonstrated an underactivity of the anterior and overactivity of the posterior lobe, this being the common formula of dysfunction. The dysfunctional thyroid cases were those in which individual evidences of both hypofunction and hyperfunction were demon-

strable in the same person. A number of these were patients in whom the gland was undergoing a functional involution from an initial overactivity to a terminal underactivity. As the various objective evidences of disturbed function do not modify with uniform speed, such transitional conditions are spontaneously synthesized and constitute true dysfunctional levels.

The ovarian group were either castrates or patients with those functional failures which correspond exactly to the picture produced by the removal of the ovaries. The adrenal patients were cases of Addison's disease, proven by autopsy, or less certainly, patients with the condition designated as "hypoadrenalism." The warrant for the inclusion of the latter has been discussed elsewhere.[14]

The pluriglandular cases were chiefly those in whom an endocrin hypofunction produced by surgical ablation was superimposed upon a functional derangement involving a second ductless gland.

The raw data from the series are collected in Table IV.

TABLE IV.—PRIMARY ANALYSIS OF ENDOCRIN GROUP.

Gland.	Function.	No.	With glycosuria.		
			No.	Per cent.	Group, per cent.
Pituitary	Hyperfunction	7	5	71.4	
	Dysfunction	367	87	23.7	
	Hypofunction	188	11	5.9	
Total	....	562	103	..	18.3
Thyroid	Hyperfunction	41	9	22.0	
	Dysfunction	92	16	17.4	
	Hypofunction	198	21	10.6	
Total	....	331	46	..	13.9
Gonad	Hypofunction	204	47	23.0	23.0
Adrenal	Hypofunction	11	6	54.5	54.5
Pluriglandular	Dysfunction	21	4	19.0	19.0
Grand total	....	1129	206	..	18.2

The number of the cases in each group is determined by the relative frequency of appearance in a consecutive series and can be considered as fairly representative. The partition of the several functional levels is not so significant as several unrelated factors influence them. The clear-cut evidences of acromegaly and exophthalmic goiter frequently render elaborate diagnostic studies unnecessary.

The percentile representation of glycosuria in the several stages of pituitary disease is striking and reflects the important part played by this gland in the regulation of one phase of the sugar metabolism. The lower incidence in the thyroid group harmonizes with the common observation of its lesser significance in sugar utilization. The seeming anomaly of glycosuria appearing with hypofunction of both the pituitary and the thyroid, conditions associated with increased assimilation limits for carbohydrate, will

be touched upon later. The figures for the other glands do no more than indicate the influence which each exercises on sugar metabolism as shown by the depression of the sugar tolerance.

The incidence of glycosuria is about the same in this group as in the important subgroups of the nonendocrin series already discussed. The large numerical contributions are from cases with pituitary dysfunction and ovarian failure, the one deriving from an overactivity, the other an underactivity of the endocrin gland involved. The highest relative frequencies are in the two small groups respectively of pituitary hyperfunction and adrenal failure. In the first the posterior lobe activity is the same in kind as in the state of dysfunction, so that a correlation is not surprising. The adrenal status parallels that of the ovary. The indication of the real influence of endocrin activity on glycosuria can best be estimated, however, when due allowance has been made for the several potentially significant nonendocrin complications.

Two of the cases with pituitary dysfunction had lesions of the central nervous system (brain tumors) and the pituitary condition was possibly only secondary to increased intracranial pressure. In addition, 4 more had well-defined psychoses, a condition also found in 1 of the cases of hypofunction.

Hepatic disease is frequently associated with functional derangement of the thyroid[15] and one-third of the present hypothyroid group demonstrated this complication. In addition, 1 more liver case was found in each of the other two groups. Two more of the hypothyroid patients were pregnant and so must be omitted from consideration. Five of the ovarian cases were significantly complicated, 1 of them being the only case of syphilis in this series. One adrenal case was psychotic.

Summarizing, nearly one-eighth of the endocrin cases present nonendocrin complications to which the glycosuria might be ascribed. Further, half of these are found in the thyroid group which had initially the smallest percentage of incidence in the endocrin series.

The findings in the endocrin group after deletion of the cases presenting complication can be presented most compactly in tabular form.

TABLE V.—SUMMARY OF UNCOMPLICATED CASES WITH GLYCOSURIA IN THE ENDOCRIN GROUP.

Gland.	No.	With glycosuria.	
		No.	Per cent.
Pituitary	562	96	17.1
Thyroid	331	33	10.0
Gonad	204	42	20.6
Adrenal	11	5	45.5
Pluriglandular	21	4	19.0
Total	1129	180	15.9

Total per cent, excluding pituitary and thyroid, failure: 21.4.

But few comments are necessary. Outside of the thyroid with a lower and the small adrenal group with a much higher level, the incidence in the remaining series approaches a parity. The relative endocrin incidence is definitely lower than that in the selected non-endocrin groups, but if the anomalous groups of pituitary and thyroid failures be eliminated, the frequency in the glandular group is about equal to that in the other. If both the endocrin and non-endocrin groups be taken in their entirety the latter shows about half as many as the former.

As already noted, true hyperglycemia is far more suggestive of the presence of diabetes than is the occurrence of glycosuria. The number of methods for blood-sugar estimation is large, and each new addition to the group tends progressively to indicate a lower level for the norm. Since its introduction in 1920, we have used the Folin-Wu[16] method, as it has proven wholly dependable and to yield reproducible results. Further, adherence to a single method of proven excellence permits of direct comparison of the results recorded over a long range of years. On the basis of this method, Joslin[9] regards a permanent fasting blood-sugar level of 130 mg. as indicative of diabetes, if a few conditions such as nephritis without hypertension, hyperthyroidism, obstructive jaundice and cardiac cirrhosis can be ruled out. The blood-sugar values obtained with the 286 cases composing this group have been collected in the next table.

TABLE VI.—BLOOD-SUGAR LEVELS OF CASES WITH GLYCOSURIA.

Nonendocrine group.			Endocrine group.		
Subgroup.	Average mg. per 100 cc.	Over 120 mg.	Subgroup.	Average mg. per 100 cc.	Over 120 mg.
Infections	98	0	Pituitary +	97	0
Psychoneuroses	99	0	Pituitary ±	96	3 (128 mg.)
Nervous system	94	0	Pituitary −	103	0
Metabolism	87	0	Thyroid +	90	1 (125 mg.)
Cardiovascular	107	1 (140 mg.)	Thyroid ±	99	0
Blood diseases	94	0	Thyroid −	99	1 (148 mg.)
Tumors	95	0	Gonad −	100	3 (125 mg.)
Ear diseases	85	0	Adrenal −	81	0
Asthma	71*	0	Pluriglandular ±	96	0
Liver diseases	96	0			
Syphilis	106	1 (142 mg.)			
Normal	101	0			
Total	97	2 (Av., 141 mg.) 2.5 per cent	Total	97	8 (Av., 129 mg.) 3.9 per cent

* The case already noted.

In the main, it is clearly apparent that high blood sugars play no significant rôle in the determination of the glycosurias. But 10 exceed the conventional limit of 120 mg. and only 4 are above the Joslin critical level. These were:

1. *Case S*-432. Pituitary dysfunction probably secondary to an established brain tumor. Blood sugar, 133 mg. Galactose tolerance, −25 per cent.

2. *Case B*-468. Syphilis complicated by nephritis without hypertension. Blood sugar, 142 mg. Galactose tolerance, ±0.

3. *Case S*-1697. Hypertension with renal involvement. Several suggestions of neurosyphilis but lumbar puncture refused. Blood sugar, 140 mg. Galactose tolerance, −67 per cent.

4. *Case S*-1677. Thyroid failure without myxedema. Request for repetition of blood sugar refused. Blood sugar, 148. Galactose tolerance, ±0 per cent.

But 1 of the cases carries any real suggestion of a possible diabetes, and this was the only one in which the blood-sugar level was not substantiated. Later reports on this patient record complete clinical improvement under thyroid medication.

In the remaining 6 cases, whose levels were superior to 120 mg., an emotional element was present in some if not all of them.*

As individual values are absorbed in collective presentation, it should be added that the only patients showing hypoglycemic levels were in the adrenal group, where it is pathognomic, the single case of asthma under heavy suprarenin medication and the following 4 cases:

1. *Case B*-127. Pituitary dysfunction. Acromegaly undergoing functional involution. Blood sugar, 73 mg. Galactose tolerance, −67 per cent.

2. *Case B*-157. Pituitary dysfunction. Facial hemiatrophy. Blood sugar, 74 mg. Galactose tolerance, −75 per cent.

3. *Case B*-112. Traumatic lesion of central nervous system. Blood sugar, 75 mg. Galactose tolerance, −33 per cent.

4. *Case B*-140. Osteitis deformans. Mitral stenosis. Nephritis. Blood sugar, 75 mg. Galactose tolerance, −87 per cent.

For the great majority of the patients the individual levels were in reasonable approximation to the group averages. The latter are to be regarded as truly representative. For such information as is intrinsic in them, these blood-sugar values generally deny the existence of diabetes in this series of glycosurics.

* In this connection, the results obtained with a medical student some years ago are suggestive. The individual in question was a highly emotional Porto Rican whose blood chemistry was determined in the course of a routine examination. The first level of 163 mg. led to weekly examinations, under exactly the same conditions. These gave successively 148, 124 and 110 mg. His habituation to venipuncture failed to dispel his distaste for it and the series was discontinued with the attainment of a normal level.

The galactose tolerance gives information as to certain aspects of the carbohydrate metabolism. Although it is a hexose, a sugar not foreign to the usual dietary, a glycogen former and presumptively a product synthesized by the mammary glands during lactation, it seems reasonably certain that its metabolism does not parallel that of glucose in all details, although in certain general respects it differs only in degree. The present analysis is concerned with the possible origins of a glycosuria that may not be traced to pancreatic hypofunction. The assimilation limits for galactose are germane to the thesis. Not all of the patients in the series received the test which requires three days for its performance. Further, the cases presenting significant complication have been deleted. Even with these limitations, practically 70 per cent of the remaining group were examined and the results of the tests are given in the next table. To save space, only the significant groups in the nonendocrin series are included. Of the 23 cases omitted, 12 did not receive the test, 5 were normal and the remaining 6 showed an average tolerance 58 per cent below prediction.

TABLE VII.—GALACTOSE TOLERANCE OF UNCOMPLICATED CASES IN THE MAJOR GROUPS.

Condition.		Tolerance.					
		Depressed.		Normal.	Increased.		Summation, per cent.
		No.	Per cent.		No.	Per cent.	
Psychoses		1	−67	..	..	..	−67
Nervous system		18	−52	3	1	+50	−40
Blood diseases		3	−50	1	..	..	−37
Tumors, malignant		3	−42	1	..	..	−31
Liver diseases		12	−56	2	..	..	−48
Syphilis		6	−40	2	..	..	−30
		43	−52	9	1	+50	−41
Pituitary	+	5	−67	..	..	..	−67
	±	56	−55	..	..	..	−55
	−	..	..	..	10	+65	+65
Thyroid	+	1	−75	..	..	..	−75
	±	3	−33	4	..	..	−14
	−	..	..	6	2	+38	+ 9
Gonad	−	20	−44	1	..	..	−41
Adrenal	−	5	−61	..	..	..	−61
Pluriglandular	±	2	−67	1	..	..	−44

In the nonendocrin group the prevailing tendency is toward a depressed tolerance, although about one-sixth were normal. The single patient showing a tolerance above prediction was a case of the Parkinsonian syndrome following an earlier encephalitis. The urine sugar was verified as glucose. Detailed study gave no evidence of any complication which could account for the anomaly.

The larger part of the endocrin cases showed a depressed tolerance

as was to be anticipated from the functional levels of the glands involved. The majority of the normal cases were in the thyroid group, this gland exercising less influence on the galactose tolerance than the other members of the endocrin concert. The single ovarian patient with a normal tolerance was one with an established nephritic condition and lowered kidney permeability. She had had both ovaries removed some years previously, so that no question could arise as to the presenting endocrinopathy. The normal pluriglandular case presented a thyroid dysfunction superimposed upon an ovarian failure deriving from castration. The galactose tolerance of the female castrate is that of prepubertal years, namely, 20 gm., and the positive response of this patient to that dosage indicated only that the thyroid dysfunction was without significant influence, a somewhat usual finding.

The two groups of major interest in this connection are, however, those patients with failure of the pituitary and thyroid respectively. Only 2 of the latter demonstrated increased levels of tolerance and the remainder were normal. The blood-sugar levels were normal with the single exception noted above (Case S-1677) and omitting this case, the group average would be 97 mg.

Far more striking are the results with the group of bilobar pituitary failures. One of the original 11, with a tolerance of +50 per cent, presented a complicating psychosis and has been deleted. The remaining 10, however, exhibited a tolerance for galactose ranging from 33 to 100 per cent above prediction with an average of +65 per cent. In spite of this increased assimilation limit—and uniformly normal blood-sugar levels throughout—all of these patients exhibited a slight but definite glycosuria. That the different sugars imply different mechanisms is obvious, but this does not resolve the question. The whole matter will be discussed in a later communication; the fact is presented here without further comment.

There remains one other condition which should be considered in this connection. Several cases have been dropped from the preceding series on the basis of pregnancy and this condition is generally recognized as productive of an intermittent glycosuria which is due to a leakage of glucose. Lactosuria does not enter the picture normally until a few days before delivery.[5]

The figures from a small group of cases may be presented for the sake of completeness. In a series of 100 patients, studied throughout their pregnancies, 18 showed glycosuria. While these figures are slightly higher than those usually recorded, the patients in the group were examined at frequent intervals. Twelve per cent gave repeated positive tests, a figure harmonizing with other reports. None of the blood sugars exceeded 100 mg. and a few fell slightly below the conventional lower boundary of 80 mg. The average

was the low normal value of 83 mg. The sugar tolerances were in all cases below the normal for an adult woman in a state of sexual rest and agreed exactly with the data of a much larger series now in process of completion. Here, again, while it is demonstrable that diabetes may develop during pregnancy or coëxist with it, it is equally true that a certain number of pregnant women exhibit a transitory glycosuria who neither at the time nor subsequently offer any evidence of pancreatic involvement.

Discussion. The whole question is both large and highly complex. No adequate treatment of even a significant number of the ramifications may find place in a journal article. A brief discussion of a small group of implications may, however, be permitted. Ignoring completely the extremely interesting and suggestive group of non-endocrin conditions associated with glycosuria, certain of the endocrin aspects only will be considered.

In the first place it is demonstrable that the pituitary has a greater quantitative influence on sugar metabolisms than any of the other endocrin glands exclusive of the pancreas. Further, in demonstrated overactivity of the pituitary glands—for morphologically and functionally the pituitary is not a unitary structure—there is a marked depression of sugar tolerance, a slight persistent glycosuria and usually a normal blood sugar, features not uniformly characteristic of diabetes. Let us assume for the moment that one or more of the pituitary hormones exercise an antagonistic effect on insulin activity and that the results of overproduction operate through this mechanism.* It would then seem that conversely, in established hypofunction, large excess quantities of insulin should be released and the insulin effects greatly augmented. But the hypopituitary case shows none of the well-known features of hyperinsulinism. Most importantly there is no hypoglycemia. On this assumption, one is constrained to conclude either that the production of insulin is depressed, a condition in ill accord with the fact of greatly increased sugar tolerance, or that the increase in available insulin augments selectively the normal processes for the disposal of carbohydrate. But analysis of this conclusion leads to further stumbling blocks. Exclusive of the direct elimination of excess sugar by the kidney, which does not come into question in this particular case, there are but three possible mechanisms which may be brought into play. The first, storage as sugar or glycogen, has very definite limits, as the body does not possess unbounded capacity for the retention of carbohydrate. The second, combustion, is equally limited as the energic requirements of the body are straitly defined and can be

* Even in this there is a large measure of assumption. In the Cushing and Davidoff experiments[7] their 3 diabetic acromegalics had shown a normal response to insulin and only failed to give the expected fall in blood sugar when the insulin was mixed with pituitrin before injection.

accurately measured. Cases of pituitary failure are not infrequently encountered which can tolerate in a single test meal enough carbohydrate to provide the total energy for the entire twenty-four-hour requirement. The third, transformation of carbohydrate into fat, offers large possibilities in providing for an excess of carbohydrates, and there is some evidence that insulin will promote fat storage. Further, there is reason to believe that under certain conditions, insulin may be concerned in the transformation of sugar into fat. That it is an usual feature of insulin activity, however, may be questioned. Certainly, high respiratory quotients are not characteristic of pituitary failure. Without adducing a number of other contradictory evidences, it may be pointed out that glandular hypofunction is a chronic state and cannot be compared or contrasted with acute conditions produced by experimentation.

A similar antagonism for suprarenin toward insulin has been demonstrated by several and in this report come yet other seeming obstacles. Addison's disease, with destruction of the glands demonstrated at autopsy, may reasonably be regarded as involving an hypofunction of the adrenals, though possibly including other factors in the complete picture. Underfunction should produce low blood sugar by a lowering of the inhibition of insulin activity and as a matter of fact, hypoglycemia is pathognomic of the condition. But, unfortunately, it should also raise the sugar tolerance—and controlled experience demonstrates that the converse is the case.

As stated at the beginning of this discussion, the problem is a vast one and even a very partial discussion would far exceed any permissible limits.

It seems warrantable to conclude, however, from the facts set forth in this paper, that the appearance of sugar in the urine is but a single end result of a large number of causes. Further, many of these can with difficulty, if at all, be interpreted as operating through the mechanism that produces the same end result in pancreatic diabetes. That insulin after it has left the pancreas or any of the body storage places may be involved in some of the other glycosurias may be freely conceded, but that it is the decisive factor in all must be equally definitely denied.

Summary. 1. The etiologic background has been studied of a number of cases showing glycosuria but without demonstrable evidence of a diabetic condition.

2. Certain nonendocrin states, including psychoses, lesions of the central nervous system, primary anemia, lymphatic leukemia, malignant neoplasm, various types of hepatic dysfunction and syphilis, have shown a distinctive frequency of incidence of glycosuria. Further, certain of these conditions have appeared as complicating factors, in a group of patients with glycosuria whose primary complaint was not included in the list given above.

3. Analysis of a similar series of disturbed endocrin functional states shows a similar incidence of glycosuria, even after those have been deleted which present the significant nonendocrin disorders as secondary complications.

4. With but minor exception, all of the individuals show normal blood-sugar levels and the several group averages are entirely within conventional limits.

5. The majority of the patients in the series show a depressed tolerance for galactose which is characteristic of the several conditions involved.

6. Exception to the foregoing is noted in the case of thyroid failure, and far more strikingly in hypofunction of the pituitary, where increased galactose tolerance is occasionally associated with glycosuria.

7. The same condition of glycosuria with normal blood sugar is noted in the physiologic state of pregnancy.

Conclusion. 1. It is concluded, that the phenomenon of glycosuria is no more than one common end result of a wide variety of causes, many of which cannot be demonstrated to produce the effect through influence on or by the function of the pancreas.

2. From this it is deduced that there are a number of factors concerned with the regulation of carbohydrate metabolism, of which the intrinsic function level of the islands of Langerhans, although most important, is but one.

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EMOTIONAL HYPERTENSION.

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It has long been known that emotional stimuli cause variations in the arterial tension. These variations are encountered both with conscious and subconscious emotional changes. During sleep the systolic arterial tension falls, usually as much as 20 mm.[1,2,3,4,5] When sleep is restless and disturbed by dreams extraordinary elevations in arterial tension have been recorded.[6] Such marked and rapid fluctuations as may occur during restless sleep constitute a very real menace to individuals with hypertension in whom the sudden rise may be responsible for cerebral, pulmonary or gastrointestinal hemorrhages.[6] The emotional state when awake plays an important rôle in the causation of temporary fluctuations in the blood pressure. The observation that the arterial tension is higher on the first visit of a patient than at later periods is common knowledge. Frequently the blood pressure is found considerably higher by an examiner for a life insurance company than the applicant's own physician ever finds it. This is largely because of the emotional tension attendant to such examinations.

The rise in arterial tension associated with emotional excitement is exaggerated in individuals with vascular disease and arterial hypertension. The most frequent factors in producing temporary arterial hypertension in young individuals are nervousness and excitement.[7] Notable increases in blood pressure occur in psychoneurotic individuals under mental strain or with anxiety neuroses.[8,9] The diastolic tension in epilepsy is extremely labile.[10] Moderate variations are noted in normal individuals if frequent repeated observations are made.[11] No positive correlation is found between the height of the blood pressure and its variability.[12]

The variations in arterial tension discussed above are notably asymptomatic. Change in arterial tonus with resultant fluctuation in the peripheral resistance to the circulation is dependent upon vasomotor stimuli. Emotional vasoconstriction or dilatation may be quite localized, as shown by the facial blanching or blushing upon fear or embarrassment. The ordinary blush, however, is not associated with any gross change in the general systemic blood pressure. It is unnecessary here to consider the neurologic control of the vascular tone and its mechanism; it suffices to state that vasomotor stimuli may arise from emotional activity and cause distinct elevation of the systemic arterial tension.

Exaggeration of a physiologic phenomenon may form a pathologic

phenomenon. Minor fluctuations of 15 to 20 mm. of pressure occurring under conditions of psychic strain are normally physiologic.[11,12] Extreme instability of the arterial tone, resulting in such exaggerated responses as fluctuations of 50 mm. or more in the arterial tension can no longer be considered physiologic. It is with such instances of vasomotor instability that the present report deals. The subjective manifestations of this interesting neurocirculatory phenomena are so variable that careful observation is often necessary to elicit the real foundation for the complaints.

Analyses of Cases. During the last year it has been our privilege to see and study 8 cases of extreme vascular instability associated with emotional hypertension. Of these cases, 7 were women. The average age was thirty-seven years, the maximum age being fifty-three and the minimum age twenty-five years. All the patients had normal arterial tension when at rest. The average blood pressure for the group was 126/80 at rest and 173/109 after psychic excitement. In all instances this psychic hypertonia was associated with definite subjective distress. In 6 out of the 8 cases the subjective distress constituted the reason for seeking medical advice. Such an average rise in arterial tension of 47/29 on mental excitement surely must be considered pathologic. The maximum rise in any patient under the stress of emotional strain was 60/32.

As many of these patients complained of emotional instability, a possible connection of the vasomotor instability with hyperthyroidism was considered likely.[13] Such a connection does not exist, however, as in 5 particularly suspicious instances in the series, determination of the basal metabolic rate revealed rates well within normal limits.

The subjective complaints are enumerated below:

SUBJECTIVE COMPLAINTS IN 8 CASES OF EMOTIONAL HYPERTENSION.

Emotional instability	5
Sexual abnormalities	6
Urticarial blotching on emotional strain	2
Flushing and sense of heat on emotional strain	2
Precordial constriction on emotional strain	2
Precordial pain on emotional strain	1
Choking sensations in throat on emotional strain	1
Epigastric distress on emotional strain	1
Cephalalgia on emotional strain	1
Apokamnosis on emotional strain	1

The relationship of sexual abnormalities is particularly interesting. All the 6 instances of abnormality occurred in women. In 3 a distressing borderline nymphomania occurred; 2 complained of frigidity, 2 had been sterile for three or four years, although they wanted children; 1 had had the pelvic organs removed with an artificial menopause. A relationship of ovarian activity and change in the arterial tension is frequently observed also in instances of

excessive masturbation.[14] The vascular instability associated with the menopause is well known.[15,16] It is probable that some physiologic connection exists between gonadal activity and the stability of vasomotor control.[17] Any relationship to the adrenal secretion of epinephrin is doubtful, as it has been shown that intense and prolonged emotional disturbance causes no effect upon the store of epinephrin, although numerous drugs diminish it greatly.[18]

The symptomatology is best illustrated by specific case reports. Four of these suffice to reveal the type of clinical pictures met with and to emphasize the variability of the presenting symptoms. One factor is common to all—the presenting symptoms are brought on by emotional strain and not by exertion.

Case Reports. CASE I.—(P.A.H.1.) A young married woman, aged twenty-six years, with a ten months' old baby, complained of a continuous sense of nervous tension with much emotional instability. Prior to her marriage she had been conscious of sexual repression and now suffered from a mild nymphomania. Had marked and uncontrollable phobias for crowds, elevators, trains and automobiles with a sense of panic. On such panic, on embarrassment or with unsatisfied sexual desire, she noted what she called "heart attacks." These never occurred with exertion, even on climbing three flights of stairs carrying the baby, although during her college life she was forbidden gymnasium work because of presumed cardiac disease. The attacks were said to consist of a sense of compression in the chest with a slow, pounding palpitation and some slight air hunger. There was no aura and the precordial distress lasted ten to fifteen minutes.

During 1918 she had suffered from a severe influenza. Her pregnancy in 1927 was uneventful except for severe hemorrhage on delivery because of a placenta previa. Habits were excellent. Examination revealed no evidence of cardiac disease. The pulse was 88, regular and no cardiac enlargement, murmurs or thrills could be elicited. The arterial tension was 130/85. On embarrassment the patient immediately complained of having an "attack;" the arterial tension was then 190/120. The urine was normal; the hemoglobin, 80 per cent (Dare). The basal metabolic rate was +5. Her response to exertion was good.

Reassurance to the effect that there was no cardiac disease and explanation of her distress assisted in calming some of the emotional instability and panic. On a second occasion, a week after the first observation, the blood pressure rose from 120/70 to 180/108 on excitement. Patient was given bismuth subnitrate (10 gr.), three times daily. In two months the distressing symptoms of panic and precordial distress had completely subsided and the instability of the arterial tension was much reduced—rising from 120/70 to 135/85 on emotional strain.

CASE II.—(P.A.H. 2.) A married woman, aged fifty-three years, complained of flushing about the head, vertigo, palpitation with tachycardia and cardiac consciousness occurring on emotional strain. Menopause had been induced by radium ten years previously. In 1918 the patient suffered severely from influenza with a considerable degree of residual myocarditis as a sequel. Chronic constipation and an irritable colon had been present for years. Habits were excellent.

Physical examination revealed nothing of moment. The heart was normal to percussion and auscultation, and exertion caused no undue distress. The arterial tension was 130/90 but with the stimulus of fright rose

to 170/110, with typical vertigo, precordial distress and tachycardia, as described above. The basal metabolic rate was −19. Therapy with Lugol's solution and bismuth subnitrate, 10 gr., three times a day, gradually gave complete relief. To date there has been no recurrence.

CASE III.—(P.A.H. 7.) A young, unmarried woman, aged twenty-eight years, complained of great emotional instability and a sense of continuous tension. On emotional reaction she was much distressed by the appearance of large urticarial blotches about the throat and chest, which persisted for ten to fifteen minutes. Occasionally emotional strain produced acute sense of heat about the head. Past history essentially uneventful. Familial environment had been that of great nervous tension. Had been most unhappy as a girl, resorting to moderate masturbation. Since maturity has been distressed by sexual impotence and leucorrhea.

Physical examination revealed nothing of moment, other than the instability of the vascular tension. At rest this was 120/70 but rose to 158/108 with merely slight psychic stimulus. Anemia was present, the hemoglobin being but 62 per cent (Dare).

Therapy with bismuth subnitrate, as in the other patients, led to a great reduction in emotional instability and the associated vasomotor phenomena which distressed her. The patient became much calmer and found herself more capable of concentration in her work as an actress. The instability in vascular tone was simultaneously reduced.

CASE IV.—(P.A.H. 5.) A young divorcee, aged twenty-nine years, active in business, was first seen in June, 1929, complaining of severe attacks of "choking," which consisted of a sense of severe constriction in the throat, air hunger and precordial oppression. These attacks were not associated with exertion, but with any excitement and particularly erotic emotions. For many years the patient had noted emotional instability and some undue dyspnea upon exertion.

The past history was unilluminating except for the admission of similar attacks previously at the time of mental strain associated with her divorce. Had always been sexually conscious and had encountered much difficulty in repressing the tendency to nymphomania. One sister is a pronounced nymphomaniac. Examination revealed a slightly enlarged, soft, symmetrical thyroid but no tremor, exophthalmos or tachycardia. The pulse was 84; the basal metabolic rate was +9. Examination of the heart revealed no abnormalities. The arterial tension was 120/70, but rose suddenly to 180/102 with acute choking distress on discussion of erotic problems. Later a spontaneous attack of distress occurred, at which time the arterial tension was 170/102. The charting of respirations during the basal metabolism test showed three regular cycles of hyperpnea which were not related to physical activity.

Therapy with bismuth subnitrate led to moderate improvement, but complete relief from all the distressing symptoms occurred when erotic stimulation was avoided.

Comment. The pathogenesis of this emotional vasomotor instability is not clear. In some way the normal equilibratory mechanism of the circulation is disturbed and an exaggerated, uncompensated response of generalized vasoconstriction occurs on psychic stimulation. The chief source of change in the peripheral resistance to the circulation, or the diastolic pressure, lies in arteriolar constriction. This constriction is dependent upon a constant flow of

impulses along the sympathetic nerve fibers to the smooth muscle in the arterial walls. Vasomotor nerves contain both constrictor and dilator fibers.[19] Hypertension may be defined as an "irritable vasomotor condition."[20] In so-called "essential" hypertension the arteriolar hypertension becomes relatively continuous. Not so here, for under conditions of psychic rest these patients all displayed normal blood pressures.

In addition to the extreme lability of the vasomotor apparatus as observed in these patients, the factor of habit must be given consideration. It has been pointed out that a vessel by constant use of its power of contraction may acquire the habit of so responding to the same degree when the stimulus is lessened or when another form of stimulus is received.[21] Fatigue of the arteriolar musculature increases its irritability[17] and so exerts an influence in the perpetuation of this instability.

Heredity may play some rôle in the production of such arterial instability,[22] as the majority of these patients are emotionally similar. They are tense, absorbed, unable to relax and often depressed.[23] Physical characteristics are not noteworthy. Endocrinologic faults of hereditary origin are not unlikely etiologic factors. No clinical evidence of adrenal dysfunction was encountered in these patients. That hyperthyroidism is not a factor is indicated by the normality of the basal metabolic rates of these patients. There does appear to be a rather close relationship to gonadal activity, however. It has been observed that the average blood pressure of women with abnormal menstrual function is higher than in the normal.[24] It is probable that at least some part of the ovarian hormone acts to reduce arterial hypertonia. The symptomatology presented by this series of patients with acute emotional hypertension rather closely resembles that of the climacteric.[15] Only 1 patient of the series, however, had reached the menopause.

As yet, it is impossible to say whether the primary fault lies in an inherent emotional or psychic instability with constant turmoil or whether this emotional instability results from the circulatory disturbance. An identical question is presented by the restless mental flutter and inability to concentrate in long-standing arterial hypertension.[17] In therapeutic attack upon both problems the results are very similar whether emotional sedatives, such as sodium bromid, or vascular sedatives, as bismuth subnitrate, are employed.[26,27] Reassurance and intimate coöperation between patient and physician can do much to calm the troubled waters of emotional storms.[25] Control of the emotional tension by physical rest is neither practical nor effective in instances such as these. Small doses of sodium bromid, 10 gr., three times per day, as used in the therapy of persistent hypertension,[28] are of some value. Attention to the gonadal factor with organotherapy should theoretically be a most important mode of therapeutic attack, but so little is known and so much

surmised regarding the hormones of the sex glands that as yet there is no rational therapeutic agent available.

In our own experience, better and more permanent therapeutic results are obtained in hypertension of spastic origin with bismuth subnitrate as a vascular sedative.[26,27] The pharmacodynamic action of bismuth subnitrate is that of minute continuous doses of nitrite ions. Instead of the violent, fleeting, quickly transient, vasodilatation obtained with the soluble amyl nitrite or nitroglycerol, a prolonged and persistent arterial relaxation occurs. Bismuth subnitrate is but very slowly soluble, so that a continuous liberation of NO_3 occurs in the bowel; in the presence of Bacillus coli the NO_3 is reduced to NO_2.[26] Through such persistent, mild vascular relaxation by the nitrite ions vascular rest reduces the arteriolar irritability. As in angina pectoris,[27] the value of bismuth subnitrate in these instances of vasomotor instability is in part prophylactic, in acting as a snubber to the spastic, erratically contracting arterioles. It offers the most physiologic type of therapy here.[29]

The symptoms presented by these patients are all directly attributable to circulatory disturbances. The one common characteristic is the association of these disturbances with emotional reactions, particularly with fear, anger, dread or erotic storms. In this respect the cardiac symptoms, such as precordial distress, thoracic constriction, palpitation, dyspnea or choking may be sharply differentiated from those arising from true cardiac disease. With reduction of the cardiac reserve, distress arises upon exertion, not upon psychic effort. The cutaneous symptoms of urticarial flushing and asymmetric perspiration are the result of local vasomotor disturbance. It is possible that the severe choking sensation complained of by one patient (Case IV) was in part due to angioneurotic edema of the upper respiratory passages. Cyanosis of the hands has been reported as being a valuable presumptive sign of hypertension.[30] Vertigo and cephalalgia during these vascular crises are undoubtedly due to impairment of the cerebral circulation.

The prognosis in such emotional hyperpiesia is as yet unsettled. This characteristic picture probably represents the earliest stage in the development of so-called "essential" hypertension. A permanent hypertension may later develop on a basis of such unusual nervous and vasomotor irritability.[31] The majority of patients with hypertension reveal the so-called nervous temperament.[32] The later anatomic changes in the arterial structures occurring in persistent hypertension are most probably the result of continued hypertonia.[33,34,35,36] Early correction of emotional hypertension apparently prevents any permanent vascular damage, but recurrences must be watched for. It is suggested that this form of disturbed vascular tension should be considered as "potential arterial hypertension." Such extreme vasomotor instability represents a precursor to vascular disease with arterial hypertension. Per-

sistence of hypertonia leads inevitably to fatigue of the arteriolar musculature and, with fatigue, hyperirritability occurs and, therefore more spasticity and additional fatigue. Thus a vicious circle is set in motion, which probably is a most significant "perpetuating factor" in the pathogenesis of arterial hypertension.[17]

Summary. Exaggeration of the vasomotor response to emotional stimulation causes an acute arterial hypertension in certain patients, with associated subjective symptoms. The rise in arterial tension is so marked as to constitute a definite menace to physical health. The symptoms are quite variable, being referable to the cardiac apparatus, the head, cutaneous sensations and the respiratory functions. The symptoms are all physiologically dependent upon vasomotor phenomena. Emotional instability is characteristic of this group. Sexual disturbances are likewise frequent and notable.

Such emotional hypertension may form the basis of later permanent arterial hypertonia. It, therefore, may well be considered as a "potential hypertension." This clinical syndrome must be sought for by blood-pressure observations, in all instances where patients complain of physical distress attendant upon psychic strain. The emotional instability so characteristic of these vasomotor phenomena may be the result of the circulatory instability, or *vice versa*. Thus far, the most satisfactory method of therapy has been the administration of bismuth subnitrate in 10-gr. doses, thrice daily, as a vascular sedative and depressant, combined with reassurance. It is important that these patients be thoroughly convinced that they are not suffering from heart disease, as many of them believe.

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THE ARTHRITIC COMPLICATIONS OF GONORRHEA IN THE ADULT MALE.

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There is division of opinion concerning the rôle of the urethral infection in the etiology of gonorrheal arthritis. There are two views: (1) That the arthritis is a manifestation of a gonococcal septicemia; (2) that the arthritis is a distant result of focal infection in prostate or seminal vesicles.

According to the first view, gonorrheal arthritis is comparable to arthritis developing during the course of pyogenic infections, pneumonia and other infectious diseases. The factors concerned are the virulence of the organisms and the resistance of the patients.

According to the second view, gonorrheal arthritis follows extension of the urethral infection to the prostate and seminal vesicles.

Methods of treatment are numerous. As they are all based on either of the above theories, they may be divided into nonfocal and focal measures.

Some examples of nonfocal measures are: (1) Vaccines and foreign proteins to promote antibody formation; (2) immobilization of the affected joints—on the grounds that the gonococcal infection is self-limited; (3) the use of heat, diathermy or irrigation through

surgical incision of the joint capsule to destroy the organisms around the joints.

Focal measures are represented by seminal vesiculotomy; seminal vesiculectomy; medication of the vesicles by various means; massage of the prostate and vesicles.

The current literature of the disease deals mainly with the value of particular methods of treatment. Good results have been obtained in some cases with every method. Usually the immediate result is considered the measure of effectiveness. There is a tendency to ignore clinical types; to credit cures to the remedy and bad results to the obstinacy of the disease.

It is well to remember that all the clinical characteristics of gonorrheal arthritis were described before the discovery of the gonococcus. They were thoroughly studied by observers who believed in the specific nature of the affection, as opposed to those who doubted the likelihood of gonorrhea being the cause of a distinct form of "rheumatism." After the discovery of the gonococcus these clinical features were considered gonococcal in the sense that gonococci cause a form of arthritis that differs, in some respects, from that caused by other bacteria.

The rôle of the urethral infection in the etiology of gonorrheal arthritis can be determined only by study of these clinical features with relation to the focal theory, that is, by clinical investigation of the urologic lesions associated with the various types of arthritis.

This paper consists of a study of 28 cases from this standpoint.

Case Reports. CASES IN WHICH ARTHRITIS DEVELOPED DURING ACUTE GONORRHEA. CASE I.—Nine days after gonorrhea, patient developed chill followed by temperature of 103° F.; left hand swollen and painful. Patient examined following day; circumscribed area over extensor tendons of left hand swollen, hot, red, painful and tender; seminal vesicles not palpable; prostate slightly soft and felt hot. Patient advised to stay in bed; no local treatment. Next day the temperature was normal and arthritis subsiding; four days later the hand was normal. The urethritis responded to routine treatment.

One year later, no recurrence of arthritis; prostate normal, vesicles not palpable; secretion normal.

Comment. The acute onset of the arthritis and the heat over the prostate suggests that absorption in this case was from the prostatic urethra. Rest in bed was sufficient to cause subsidence. No other similar case has been encountered.

CASE II.—Seventeen days after gonorrhea, lumbar back painful on motion and at rest unless supported; right knee painful on motion but not swollen or discolored. Roentgen ray; no pathologic bone changes. Prostate slightly boggy; seminal vesicles palpable but not hot. Treatment consisted of urinary sedatives and hot sitz bath twice daily. Arthritis subsided in three days; urethritis responded to treatment. One year later, no recurrence of arthritis; prostate normal; vesicles not palpable; secretion normal.

CASE III—Seventeen days after gonorrhea, dorsal aspect left wrist and metacarpophalangeal joint of left thumb painful and slightly swollen; no

heat or discoloration. Prostate slightly soft; both vesicles palpable but not hot; paraphymosis. Treatment, paraphymosis reduced; hot sitz bath twice daily. Arthritis subsided in four days. Six months later, no recurrence of arthritis; prostate slightly soft; vesicles not palpable; secretion, living spermatozoa, 40 to 50 pus cells to high-power field.

CASE IV.—Twenty days after gonorrhea, dorsal aspect of left wrist painful and slightly swollen; left knee painful on weight bearing; slight swelling of both sides of patella. Prostate slightly soft; left vesicle palpable; right vesicle not palpable. Treatment, hot sitz bath twice daily. Arthritis subsided in four days. Four months later patient contracted another gonorrhea, seminal vesicles not palpable, no arthritis. One year later, no recurrence of arthritis, prostate slightly soft, vesicles not palpable, secretion, living spermatozoa, 15 to 20 pus cells to high-power field.

Comment on Cases II, III and IV. In these cases the affected joints were painful; but swelling, when present, was slight, and there was no heat or redness. Both seminal vesicles were palpable in Cases II and III and the left vesicle was palpable in Case IV; heat was not noted over the vesicles in any of these cases. The arthritis subsided in all cases in a few days.

The acute joint inflammation of gonorrheal arthritis is often preceded by pain and slight swelling of the joints. Cases such as these, in which the joint involvement subsides instead of advancing to the stage of acute inflammation, are occasionally encountered. They may form the basis for claims for effectiveness of various remedies in checking the advance of gonorrheal arthritis.

The explanation offered here is that the arthritis subsided because the process in the vesicles subsided and absorption stopped. Had the involvement of the vesicles continued to the stage of acute seminal vesiculitis the joints would have become acutely inflamed.

CASE V.—Duration, three days. Acute inflammation of extensor tendons of right hand and wrists; right knee painful on motion. Seminal vesicles not palpable but increased heat noted over right vesicle area.

CASE VI.—Duration, seven days. Acute inflammation of extensor tendons of left hand and wrist. Left seminal vesicle palpable and hot; right vesicle palpable.

CASE VII.—Duration, eight days. Acute inflammation of tendons over instep of left foot; both shoulders, dorsal and lumbar back painful. Both vesicles palpable and hot.

CASE VIII.—Duration, eight days. Acute inflammation of tendons around external malleolus of both feet. Both vesicles palpable and hot. Stricture of small caliber in anterior urethra.

CASE IX.—Duration, sixteen days. Acute inflammation of extensor tendons of left hand and wrist; muscles of forearm wasted. Both vesicles palpable and hot.

CASE X.—Duration, eighteen days. Acute inflammation of extensor tendons of right hand and wrist and involving flexor tendons of wrist; acute

inflammation of periarticular tissues of left ankle. Both vesicles palpable and hot.

CASE XI.—Duration, twenty-three days. Acute inflammation of extensor tendons of left hand and wrist and periarticular tissues of right ankle. Both vesicles palpable and hot.

CASE XII.—Duration, forty days. Acute inflammation of periarticular tissues of right knee, both ankles and metacarpophalangeal joint of right thumb; lumbar back and right temporomandibular joint painful on motion. Both vesicles palpable and hot.

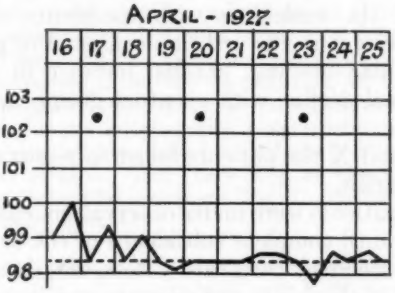

CHART I.—Temparature chart of Case XII.

Comment on Cases V, VI, VII, VIII, IX, X, XI and XII. These are typical examples of acute gonorrheal arthritis in the stage of acute joint inflammation. Gonococci were present in the urethral discharge in every case. The arthritis developed in from five to thirty-three days after gonorrhea. Roentgen-ray studies showed decalcification of the bones of the acutely inflamed joints at some time during the course of the disease.

One or more of the affected joints in each case were swollen, hot, reddened and tender. Acute inflammation of the seminal vesicles was denoted in each case by the presence of heat over one or both of these organs.

The arthritis was unilateral in Cases V, VI and IX and in Cases V and VI the acute vesiculitis was unilateral and on the same side as the arthritis. The arthritis was bilateral in Cases VII, VIII, X, XI and XII and the acute vesiculitis was bilateral in these cases.

These findings indicate that the acute arthritis is dependent upon the acute vesiculitis and that the duration of the acute joint inflammation depends upon the duration of the acute vesiculitis.

These patients were treated by the injection of Pregl's solution into the seminal vesicles through the rectal mucosa as first described by Stellwagen in 1925.[1] This procedure checked the absorption from the vesicles and in each case the acute inflammation of the

joints subsided; that is, pain became less severe, swelling decreased and heat and redness disappeared.[2] The injections were also followed by decline in the fever. It may be inferred from this action of the injections that the fever in such cases depends upon the acute vesiculitis. The temperature chart of Case XII is presented as being typical of the group.

Further treatment consisted of massage of the prostate and vesicles in order to rid these organs of infection. This was started as soon as it was thought that the vesicular inflammation had subsided sufficiently to permit of massage without danger of causing exacerbation of the vesiculitis with recurrence of the arthritis. Further improvement in the arthritis consisted of gradual decrease in the periarticular swelling, gradual increase in mobility of the joints and gradual decline with eventual disappearance of pain on motion.

In Cases VI and X the patients failed to report after subsidence of the acute arthritis.

All the other patients were under observation, either continuously or at intervals, until complete subsidence of the arthritis and were examined at subsequent intervals. Relevant data on the subsequent condition of the joints and prostate and vesicles follows:

Subsequent Condition of Cases V to XII. Case V.—One year after discharge: No symptoms of arthritis; Roentgen ray, no pathologic bone changes; secretion after massage; living spermatozoa; no excess of pus.

Case VII.—Six months after onset: No symptoms of arthritis; Roentgen ray, no pathologic bone changes; prostate soft; vesicles palpable; secretion, nonmotile spermatozoa, 100's pus cells to high-power field.

Case VIII.—One year after onset: No symptoms of arthritis; Roentgen ray, no pathologic bone changes; secretion after massage, normal; stricture dilated to 30° F.

Case IX.—Discharged from hospital in twenty days: Acute inflammation subsided, but there was marked periarticular thickening of left wrist. One year later, without subsequent treatment, slight periarticular thickening, grip normal and muscles of forearm normal; Roentgen ray, decalcification of bones and narrowing of joint space; prostate boggy; vesicles palpable; secretion, 100's pus cells; culture, pneumococci and Gram-negative bacilli belonging to the Friedländer group. Two years later, without intervening treatment, left wrist normal clinically; Roentgen ray: narrowing of the joint space and no pathologic bone changes except for fracture of lower end of radius which is united in good position. (Patient had sustained a Colles fracture.) Prostate soft; vesicles palpable; secretion, 100's pus cells.

Case XI.—One year after discharge; no symptoms of arthritis; *x*-ray, no pathologic bone changes; prostate normal, vesicles not palpable; secretion, normal.

Case XII.—Two years after discharge; no symptoms of arthritis; *x*-ray, no pathologic bone changes; prostate normal vesicles not palpable; secretion normal.

Comment. Recovery from the arthritis was complete in each of these cases. However, recovery from the arthritis should not be accepted as the sole standard of cure. Cure cannot be considered complete unless infection is eradicated from the prostate and seminal vesicles. This is illustrated in Cases V, VIII, XI and XII.

CASES IN WHICH THERE WAS PERSISTENCE OF JOINT DISABILITY AFTER GONORRHEAL ARTHRITIS. CASE XIII.—Four months after gonorrheal arthritis: Left knee still slightly swollen; restriction to full extension and flexion; muscles above and below knee wasted; patient unable to bear full weight on left knee and uses crutches; slight swelling metacarpophalangeal joint of right thumb; right shoulder painful on motion. Roentgen ray: irregular areas of marked decalcification of bones of left knee; small quantity of fluid in joint. (Figs. 1 and 2.) Prostate slightly soft; both vesicles palpable and tender; secretion, nonmotile spermatozoa, 70 to 80 pus cells to high-power field; no gonococci; culture, no growth at end of seventy-two hours. Treatment, vesicles injected with Pregl's solution; later, massage of prostate and vesicles; left knee baked in Orthopedic Department; patient resumed work in six months. Two years later, no recurrence of arthritis; Roentgen ray, no pathologic bone changes (Fig. 3); prostate normal; vesicles not palpable; secretion, normal.

CASE XIV.—Both heels painful since gonorrheal arthritis seven years ago. Operation for removal of spurs from both heels three years ago with no relief from pain. Roentgen ray: advanced hypertrophic osteoarthritis of bones of both feet. Prostate soft; vesicles palpable; secretion, nonmotile spermatozoa, 100's pus cells; culture, Staphylococcus albus.

CASE XV.—Bony ankylosis of right wrist nine months after gonorrheal arthritis which was treated by cast. Prostate slightly soft; vesicles barely palpable; secretion, nonmotile spermatozoa, 80 to 100 pus cells to high-power field.

CASE XVI.—Partial ankylosis of right wrist and metacarpophalangeal joints of right middle, ring and little fingers, three months after gonorrheal arthritis. Roentgen ray, general decalcification of the bones of the right hand and wrist; the articular cartilage between the carpal bones has been absorbed. Prostate normal; vesicles not palpable; secretion, normal.

Comment on Cases XIII, XIV, XV and XVI. A tendency to chronicity is widely believed to be a necessary clinical feature of gonorrheal arthritis.

Joint disability after the subsidence of the acute stage of the disease is due to the persistence of subacute inflammation of the joints, to ankylosis or to the gradual development of osteoarthritis. It is questionable whether these complications are always due to chronicity in spite of treatment rather than to improper treatment. Proper treatment should aim at the prevention of these complications.

The means of prevention should be sought in study of the relationship between the urologic lesions and the joint lesions. The significant fact of this relation is the association of the subsidence

of the acute joint inflammation with the subsidence of the acute vesiculitis.

In the stage of subacute joint inflammation the vesicles are palpable but not hot. Absorption from such vesicles may cause the continuance of subacute inflammation of the joints which may be followed by osteoarthritic bone changes. Osteoarthritis may also occur insidiously, that is, without inflammation of the parts.

Case XIII is an example of the continuance of subacute joint inflammation due to the continuance of absorption from the vesicles. Focal treatment resulted in complete recovery.

Measures directed solely to the joint inflammation are recommended by some writers in such cases. The good results attributed to this form of treatment are due rather to spontaneous subsidence of absorption from the vesicles. In cases in which absorption from the vesicles continues nonfocal measures, such as drainage of the joint, are apt to be followed by the tragedy of bony ankylosis.

Case XIV is an example of the development of osteoarthritis after apparent recovery from gonorrheal arthritis. This is an example of the futility of nonfocal measures (which in this case was the removal of spurs) in the presence of absorption from the vesicles. This patient had three attacks of iritis and, on medical advice, had his tonsils and several teeth removed, but was never given an examination of the prostate and vesicles.

Case XV is an example of the spontaneous subsidence of gonorrheal arthritis. Two joints were originally affected; treatment of one joint by means of a cast resulted in bony ankylosis. The patient also had persistence of infection in the vesicles. In view of the possibility of osteoarthritis from this source, the vesiculitis must be considered almost as grave a complication as the ankylosis. While it is true that not all infected vesicles are focal areas, still it is impossible to be sure that absorption will never take place.

Case XVI illustrates the tendency that the disease, at times, exhibits to spontaneous recovery. There was spontaneous subsidence of the focus and unaided eradication of infection from the prostate and vesicles.

Cases in Which Recurrence Occurred After Apparent Cure of Gonorrheal Arthritis. Case XVII.—In 1918 gonorrheal arthritis of right knee for nine months. In 1921 both ankles painful and swollen and both heels painful; unable to work since 1922. In 1924 osteophytes removed from both heels with no relief from pain.

Patient first seen, March, 1925; both heels, right knee and left shoulder painful; walks with difficulty. Prostate boggy; both vesicles palpable. Vesicles injected; later prostate and vesicles massaged. Patient returned to work in two months and did not report for further treatment.

In October, 1928, recurrence of arthritis for four weeks; metacarpophalangeal joint of left great toe painful and slightly swollen; both heels painful, interphalangeal joint of left thumb painful and slightly swollen. Roentgen ray: no pathologic changes of bones of left thumb, there is decalcification of the bones of both feet, flattening of the left os calcis, general osteo-

arthritis of the bones of the left foot, particularly the tarsal bones, osteoperiostitis of the right os calcis. Prostate slightly soft, vesicles palpable, secretion, 90 to 150 pus cells to high-power field. Arthritis again responded to focal treatment.

CASE XVIII.—In 1921 gonorrheal arthritis of both feet, knees and hips, afflicted for about eighteen months. In September, 1926, both knees and ankles swollen and slightly painful. Roentgen ray: there is a small spur on the posterior-inferior angle of the right patella and a smaller spur in the same position on the left patella, there is general decalcification of the bones of both feet with a small spur on the under surface of both os calci. (Fig. 4.) Prostate, areas of induration in both lobes, both vesicles palpable, secretion, 50 to 100 pus cells to high-power field, culture, no growth at end of seventy-two hours. Arthritis responded to focal measures.

Two years later patient had received massage of prostate and vesicles every three months, no recurrence of arthritis. Roentgen ray: there is no increase in the size of the spurs on the patella or os calci and the bones of both feet show return of normal bone salt content. (Fig. 5.)

CASE XIX.—In 1918 gonorrheal arthritis of both knees and ankles. In May, 1927, pain and slight swelling of right knee, anterior arch of right foot and left ankle. Roentgen ray: large osteophyte on the under surface of both os calci. (Fig. 6.) Prostate slightly soft, both vesicles palpable. Arthritis responded to focal treatment.

Two years later, no symptoms of arthritis. Roentgen ray: no increase in the size of the spurs. (Fig. 7.) Prostate normal, vesicles not palpable, secretion, normal.

CASE XX.—In 1919 gonorrheal arthritis of both knees and ankles; joints swollen for four months and painful for another year. In January, 1927, right ankle, both knees, left great toe and right thumb painful and swollen; arthritis gradually subsided in all joints except right thumb, although right ankle was sore and painful at times. Patient first seen, March, 1928, with right thumb painful and swollen at interphalangeal and metacarpophalangeal joints; both ankles normal clinically, but right ankle becomes sore and painful after day's work. Roentgen ray: right thumb, no pathologic bone changes; right ankle, large osteophytic spur on the anterior and external aspect of the lower end of the right tibia; decalcification of the lower end of the fibula, the external aspect of the lower end of the tibia and the external aspect of the astragalus; there is irregularity of the external aspect of the astragalus and a circular area of bone infection in the superior, external aspect of the astragalus. (Fig. 8.) Prostate normal; vesicles barely palpable; secretion, normal prostatic fluid, mucous with entangled nonmotile spermatozoa and few pus cells; culture, no growth at end of forty-eight hours. Treatment, massage once monthly.

Ten months later, right thumb normal clinically and not painful for past eight months; right ankle still sore at times. Roentgen ray: there is definite, although moderate, improvement in the osteoarthritic changes in the right ankle. There is a general increase in the bony density of the structures around the external aspect of the ankle. The external aspect of the astragalus is more regular. The chronic bone abscess cavity is slightly smaller and bone condensation has occurred around its circumference. (Fig. 9.)

CASE XXI.—In 1906, gonorrheal arthritis of ankles, knees, shoulders, wrists and elbows; in bed eighteen months and crippled four years. In 1915, recurrence in shoulders, elbows, wrists and fingers; well in about

three months. In 1927, recurrence in both shoulders, knees, wrists and left thumb; in bed two months. In May, 1928, left shoulder still painful on raising arm high; metacarpophalangeal joint of left thumb slightly swollen and painful. Roentgen ray: bursitis of left shoulder; no other pathologic bone changes. Prostate normal; vesicles not palpable; secretion, nonmotile spermatozoa, 30 to 50 pus cells to high-power field.

Comments on Cases XVII, XVIII, XIX, XX and XXI. Liability to recurrence is another clinical feature widely believed to be characteristic of gonorrheal arthritis.

The facts of the relationship between the joint lesions and the urologic lesions, as shown in the study of these cases, indicate rather that recurrence should be considered a preventable complication.

Infection was present in the seminal vesicles in all these cases.

Three features of the arthritis are worthy of mention as bearing on the focal nature of these cases: (1) Osteoarthritic bone changes were present in all but 1 case; in this one exception there was calcification of a bursæ. (2) The recurrent attacks did not always involve all the joints originally affected and often joints which were unaffected in the original attack were involved in the recurrences. (3) The inflammation of the joints in the recurrent attacks was not as acute as in the original attack.

In other words, these cases are not true recurrences of the original gonorrheal arthritis. They are instances of arthritis due to exacerbation of seminal vesiculitis which originated during the original gonorrheal arthritis. They are complicated by osteoarthritis due to insidious action of the focal lesions.

Prevention of such cases depends upon complete eradication of infection from the prostate and vesicles after acute gonorrheal arthritis.

Cases in Which Arthritis Developed After Gonorrhea Was Apparently Cured. Case XXII.—Three years after gonorrhea: Scant mucoid, urethral discharge; right ankle sore; few days later, left ankle sore; both ankles painful and swollen; both elbows and wrists and lumbar back painful. Ten days later arthritis had entirely subsided in all joints except ankles. Pain, swelling, tenderness and slight discoloration over tendons around external malleolus of both ankles. Roentgen ray: no pathologic bone changes. Prostate swollen; both vesicles palpable. Arthritis responded to focal treatment.

Two years later: No recurrence of arthritis; Roentgen ray: no pathologic bone changes. Prostate normal; vesicles not palpable; secretion, normal.

Case XXIII.—Six years after gonorrhea: Scant mucoid, urethral discharge; left epididymitis; both heels and anterior arches of both feet painful. One week later, both ankles painful and swollen; right wrist and metacarpophalangeal joint of right index finger painful and slightly swollen; both knees painful and swollen. One month later arthritis had subsided in all joints except knees and ankles. Roentgen ray: no pathologic bone changes. Prostate slightly soft; both vesicles barely palpable. Stricture of small caliber in anterior urethra. Arthritis responded to focal treatment.

One year later; no recurrence of arthritis; *x*-ray, no pathological bone changes; prostate soft, vesicles not palpable; secretion, normal. Stricture dilated to 29° F.

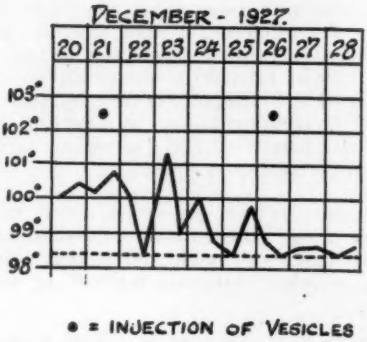

CHART II.—Temperature chart of Case XXII.

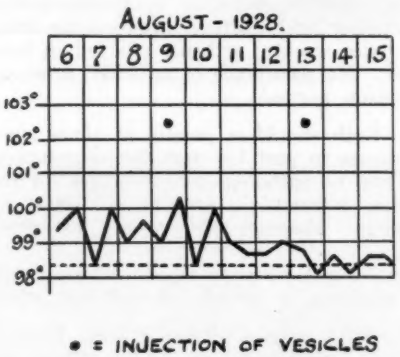

CHART III.—Temperature chart of Case XXIII.

Comment on Cases XXII and XXIII. The clinical features of the arthritis in these cases differ in no essential respect from those usually considered characteristic of gonorrheal arthritis. The affected joints were painful for a few days before swelling developed, several joints were involved and the arthritis finally settled in some of the larger joints.

Clinicians who believe that gonococci cause a distinct form of arthritis are very apt to diagnose such cases as gonorrheal arthritis, basing the diagnosis on the clinical course, the history of previous gonorrhea and, perhaps, the presence of Gram-negative extracellular diplococci in the prostatic secretion. Such a diagnosis is in error and may lead to the institution of inappropriate treatment which may be followed by grave consequences.

These cases are more properly called postgonorrheal arthritis and

are due to absorption from vesicles which have become the seat of postgonorrheal infection.

CASE XXIV.—One year after gonorrhea: Recurrent urethral discharge negative for gonococci; severe pain over right sacroiliac joint; surrounding tissues tender. Roentgen ray, some absorption of the cartilage of the right sacroiliac joint. Prostate slightly soft, both vesicles palpable and tender. Arthritis treated by injections of vesicles and later massage of prostate and vesicles. Four months later, no symptoms of arthritis, prostate slightly soft; vesicles barely palpable; secretion, 10 to 15 pus cells to high-power field; culture, Staphylococcus albus.

CASE XXV.—Three months after gonorrhea: Both shoulders and lumbar back painful in morning; pains subside somewhat during day. Prostate slightly soft; both vesicles palpable and tender; secretion, nonmotile spermatozoa, 100's pus cells. Arthritis relieved in three weeks after biweekly massage.

CASE XXVI.—Four years after gonorrhea: Both knees and both ankles painful; metacarpophalangeal joint of left thumb painful and slightly swollen. Roentgen ray: no pathologic bone changes. Prostate slightly soft; both vesicles palpable; secretion, nonmotile spermatozoa, 50 to 60 pus cells to high-power field; culture, Micrococcus ureæ, Staphylococcus albus. Massage twice weekly; arthritis relieved in three months.

Two years later: No recurrence of arthritis; prostate normal; vesicles not palpable; secretion, normal.

CASE XXVII.—Both shoulders painful at times since gonorrhea, five years ago; pains worse in past two months; no relation to movement of arms. Roentgen ray, no pathologic bone changes. Prostate soft; vesicles palpable; secretion, nonmotile spermatozoa, 100's pus cells; culture, Staphylococcus albus. Massage twice weekly, arthritis relieved in three months.

One year later: No recurrence of arthritis, prostate soft, vesicles barely palpable; secretion, nonmotile spermatozoa, 100's pus cells.

CASE XXVIII.—Fifty years after gonorrhea: Lower back painful and sore. Roentgen ray, some hypertrophic osteoarthritis of second and third lumbar vertebræ. Prostate slightly soft; vesicles not palpable; secretion, 50 to 60 pus cells to high-power field; culture, Staphylococcus albus, Streptococcus nonhemolyticus. Pain greatly relieved in few weeks by massage of prostate twice weekly.

One year later: Back sore at times; prostate slightly soft; vesicles not palpable; secretion, 50 to 60 pus cells to high-power field.

Comment on Cases XXV, XXVI, XXVII and XVIII. Infection was present in the prostate and vesicles in 4 of these cases and in the prostate only in 1 of the cases. These lesions are commonly called postgonorrheal.

It is questionable whether infection in the prostate and vesicles in such cases followed actual invasion of these organs by gonococci during the course of the gonorrhea. It may be that these lesions are due to later invasion from the posterior urethra of infection following the gonorrheal posterior urethritis.

However, arthritis from such foci may be considered largely

FIG. 1.—Case XIII. Four months after gonorrheal arthritis. There are irregular areas of marked decalcification of the bones of the left knee.

FIG. 2.—Case XIII. Same as Fig. 1, but showing distention of the joint capsule of the left knee due to fluid in joint space.

FIG. 3.—Case XIII. Two years after Fig. 2. The bones of the left knee are normal.

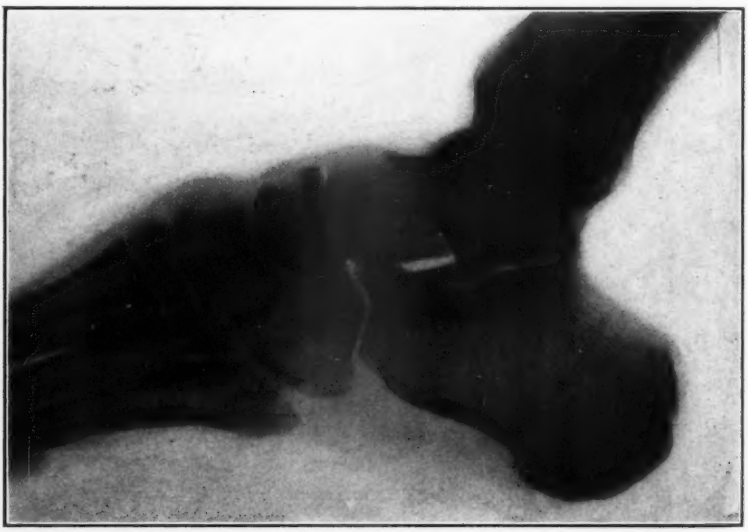

FIG. 4.—Case XVIII. There is general decalcification of the bones of the right foot with a small spur on the under surface of the os calcis.

FIG. 5.—Case XVIII. Two years after Fig. 4. The bones of the right foot show normal bone salt content. There is no increase in the size of the spur on the under surface of the os calcis.

FIG. 6.—Case XIX. There is a large spur on the under surface of the right os calcis.

FIG. 7.—Case XIX. Two years after Fig. 6. There is no increase in the size of the spur.

FIG. 8

FIG. 9

FIG. 8.—Case XX. There is decalcification of the lower end of the fibula, the external aspect of the lower end of the tibia and the external aspect of the astragalus. There is irregularity of the external aspect of the astragalus. There is a circular area of bone infection in the superior, external aspect of the astragalus.

CASE 9.—Case XX. Ten months after Fig. 8. There is definite, although moderate, improvement in the osteoarthritis of the right ankle. There is a general increase in the bony density of the structures of the external aspect of the ankle. The external aspect of the astragalus is more regular. The chronic bone abscess cavity is slightly smaller and bone condensation has occurred around its circumference.

preventable. The means of prevention consist of reëxamination of cases of gonorrhea after apparent cure to be sure that such focal lesions do not develop.

Summary. In 2 cases of this series the clinical findings indicated that the prostate was the site of the focal infection. In Case I the prostate felt hot to rectal palpation and absorption probably occurred from the prostatic urethra. The arthritis was acute. Such cases should be recognized by routine rectal examinations in gonorrheal arthritis. In Case XXVIII the arthritis developed fifty years after gonorrhea. Infection was present in the prostate but not in the vesicles.

In all the other 26 cases the clinical evidence indicated that the seminal vesicles were the site of the focal infection. The vesicles in all cases were soft. The relationship between the arthritis and the vesiculitis is shown by the following:

In 3 cases (II, III and IV) which developed during acute gonorrhea the arthritis was comparatively mild. In these cases the vesicles were palpable but not hot.

In 8 cases (V to XII) of typical acute gonorrheal arthritis the seminal vesicles were palpable and hot. The arthritis was bilateral in 5 cases in which the vesiculitis was bilateral. The arthritis was unilateral in 2 cases in which the vesiculitis was unilateral and on the same side as the arthritis. Injection of the vesicles with Pregl's solution resulted in decline in the fever and subsidence of the acute joint inflammation in all cases. The fever and acute joint inflammation apparently depend upon the acute vesiculitis. Complete cure should include eradication of infection from the prostate and vesicles.

There were 4 cases (XIII to XVI) in which joint disability followed acute gonorrheal arthritis. In 1 case there was persistence of subacute joint inflammation, due to persistence of absorption from the vesicles after the subsidence of the acute vesiculitis. In 1 case there was osteoarthritis due to absorption from infected vesicles. In 1 case there was bony ankylosis with persistence of infection in the vesicles. In 1 case there was fibrous ankylosis with spontaneous eradication of infection from the prostate and vesicles.

In 5 cases (XVII to XXI) in which arthritis developed subsequent to apparent cure of gonorrheal arthritis there was infection in the vesicles in all cases. In 4 cases there was osteoarthritis and in 1 case there was calcification of a bursæ.

There were 7 cases (XXII to XXVIII) in which arthritis developed after clinical cure of gonorrhea. In 2 of these cases the clinical features of the arthritis were such as are usually considered characteristic of gonorrheal arthritis. Infection of the vesicles was present in both cases, but the vesicles were not hot to rectal palpation. In 5 of the cases the arthritis was of the arthralgic type and associated with infection in the vesicles.

Conclusions. It would appear, then, that the clinical features of gonorrheal arthritis are due to the nature of the focal areas rather than to the nature of the gonococcus. Arthritis due to gonococcal infection of the vesicles differs from arthritis due to nongonococcal infection of the vesicles only in degree of intensity of the resulting joint lesions. The two types exhibit the same predilection of the larger joints; are both likely to involve several joints; tend to spontaneous cure of some of the involved joints with persistence in others.

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POSSIBLE ILL EFFECTS FOLLOWING INTRAVENOUS USE OF AMMONIUM ORTHO-IODOXY-BENZOATE.

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Favorable results in treatment of chronic arthritis by intravenous use of ammonium ortho-iodoxy-benzoate reported by Young and Youmans,[1,2] Smith,[3] Trauba,[4] Cottrell[5] and many others have led to rather widespread use of this method. With the exception of that of Manace,[6] who reports a fatality following the intravenous use of this drug, reports have been favorable. Mild reactions following administration of the drug have been common, and are apparently to be expected, but, with the exception of the case reported by Manace, no serious ill effects have been recorded.

It is the purpose of this report to bring before the profession an isolated disastrous experience with this method of treatment in order again to emphasize the fact that intravenous treatment may be not without danger. It will be seen from the cases herewith reported that the death of 1 patient and very serious illness of 3 others occurred in spite of the most careful precautions in preparation and administration of the drug solution.

Previous History of Cases.—CASE I.—Male, aged sixty-six years, was admitted to the medical department of the Multnomah County Hospital, June 22, 1927. The patient was suffering from a chronic deforming arthritis of one year's duration. All of the joints of both upper and lower extremities were involved in the process. All active foci of infection were removed. The patient was treated with different forms of medical and physical therapy for eight months without any lasting improvement.

CASE II.—Male, aged sixty-one years, admitted to the medical department of the Multnomah County Hospital, January 31, 1928. A diagnosis of chronic deforming arthritis was made. The joints of both upper extremities and the cervical spine were markedly involved, and the joints of both lower extremities involved to a lesser degree. Infected teeth and tonsils were removed, and a bilateral radical transantral sphenoethmoidectomy was performed. These operative procedures plus medical and physical therapy failed to give more than slight temporary improvement over a period of three months.

CASE III.—Male, aged thirty-three years, admitted to the medical department of the Multnomah County Hospital, March 7, 1928. A subacute infectious arthritis involving both knee joints was diagnosed. The present attack was of ten days' duration. A chronic gonorrheal posterior urethritis and prostatitis was thought to be the source of infection, and was treated in the genitourinary department with definite but slow improvement in the affected joints.

CASE IV.—Male, aged forty-three years, had been admitted to the Multnomah County Hospital several times previous to his admittance on April 9, 1928. The patient had a chronic gonorrheal posterior urethritis and prostatitis with recurrent attacks of gonorrheal arthritis involving the larger joints of the upper and lower extremities. On previous admittances, treatments in the genitourinary department, consisting of massage, irrigations, instillations, and so forth, had relieved the patient of joint pain and stiffness. Such local treatment was being carried on with less favorable results than on previous admittances; at the same time it was suggested that the patient be given ammonium ortho-iodoxy-benzoate.

CASE V.—Male, aged forty-six years, admitted to the Multnomah County Hospital, April, 1928. The patient gave a history of previous recurrent attacks of arthritis since 1920. The present attack was of several days' duration and involved the joints of the left lower extremity. Chronic gonorrhea, seminal vesiculitis, prostatitis and posterior urethritis, along with numerous acute gonorrheal reinfections accounted for the condition. The patient was receiving treatments in the genitourinary department at the time ammonium ortho-iodoxy-benzoate was administered.

Two different preparations of ammonium ortho-iodoxy-benzoate were administered to these patients. The following technique was used in preparation and administration of the drug: One gram of ammonium ortho-iodoxy-benzoate was dissolved in 100 cc. of normal saline solution prepared from freshly distilled water. This was injected intravenously by the gravity method, in each instance taking between twelve and fifteen minutes for administration. Fifty to 100 cc. of normal saline solution was then injected before the needle was withdrawn to prevent any possibility of local reactions at the site of injection.

The reactions observed and the results obtained, using the preparation of ammonium ortho-iodoxy-benzoate, known as oxoate (Smith, Kline & French), given intravenously, are as follows:

CASE I.—Four injections were given at four-day intervals. Reactions were noticed in about ten minutes, consisting of smarting sensation in the eyes with lacrimation, burning of the tongue, sneezing, slight salivation, increased pain and burning in the affected joints. The duration of these reactions averaged about one hour. There was no increase in temperature, pulse or respiration following administration of the drug. The results obtained were, subjectively, slight relief from pain in the joints, twenty-four to thirty-six hours after injection and objectively that a chronic conjunctivitis which the patient had had for weeks entirely disappeared after the second injection. The joints showed no changes.

CASE II.—Received four intravenous injections at four-day intervals. Reactions started in about ten minutes, consisting of smarting of the eyes and burning sensation of the tongue. Pain was greatly increased in all of the affected joints following the first two injections. The temperature which was previously normal was increased to 100° F. following the first treatment and to 99° F. following the second treatment. Following the third and fourth injections subjective relief was marked. The patient was impressed and pleased with the progress made. Objectively it was noticed that flexion and extension of the wrists and fingers and all movements of the cervical spine were actively carried out with greater freedom.

CASE III.—Received two intravenous injections at four-day intervals, showing only mild mucous membrane reactions after the first treatment. After the second treatment the patient developed a generalized toxic erythema and no further treatments were given. The joints, however, were somewhat improved.

Case IV and Case V received no treatments with "oxoate."

Another preparation of ammonium ortho-iodoxy-benzoate, manufactured by another pharmaceutical house, was then used. Cases I, II, IV and V were all given treatments the same day, using the same technique in preparation and administration of the drug as in previous treatments. The following results were noted:

CASE I.—More severe early reactions were noted than with the four previous injections. These reactions gradually became more distressing and were accompanied by abdominal cramps, vomiting, diarrhea and increased pain in the affected joints. In two and a half hours after the injection the temperature was 101° F., axilla; pulse, 124; respiration, 28. Restlessness and great anxiety was marked and headache became excruciating. The symptoms steadily increased in severity, and in spite of all efforts toward relief the patient expired eight hours after administration of the drug.

CASE II.—Again the early symptoms of burning in the eyes, mouth and nose were first noticed, as in the four previous treatments. Abdominal cramps with nausea, vomiting and watery bowel movements followed. The patient then had a severe chill, lasting forty minutes. The tempera-

ture rose to 102° F.; the pulse, 130; respiration, 30. There was extreme pain in the joints and a severe headache. These reactions lasted twelve hours. Following this, there was such a marked stomatitis and gastroenteritis that the patient was unable to eat for several days. The headache persisted for days. There was no change noted in the joints.

CASE IV.—The patient had received no previous injections. The onset of preliminary symptoms was sudden. Nausea, vomiting and headache accompanied the burning, lacrimation and salivation. There was a severe chill and the temperature increased to 101° F. The reaction lasted several hours and was followed by a marked gastroenteritis.

CASE V.—The patient had received no previous treatment. Intravenous injection of the drug was quickly followed by burning in the mouth, salivation and terrific pain in the epigastrium. There was no chill and only a slight rise in temperature. The patient suffered extreme nausea and vomiting. Headache was marked and the reaction lasted more than twelve hours.

Autopsy Record. CASE I.—(By Dr. W. C. Hunter, April 10, 1928.) This is the body of a white male (J. L.), aged sixty-six years. The body is emaciated. There is a small swelling on the lower right lid. The knee joints are enlarged and there is atrophy of the muscles of the leg and thigh.

The subcutaneous fat in the usual midline incision is 1 cm. in thickness. The cecum is seen to be distended with gas and congested. The peritoneum is smooth, moist and glistening. The small bowel is of uniform caliber. The stomach occupies the usual position. The spleen is bound down posteriorly by fibrous adhesions. The liver is at the costal margin in the right midclavicular line.

The lungs are well aërated anteriorly. The left pleural cavity is completely obliterated by old fibrous adhesions. The space occupied by the heart is increased in size. The pericardial sac contains about 50 cc. of straw-colored fluid. There is a "soldier's spot" on the anterior surface of the right ventricle about 1.5 to 2 cm. in diameter. When the heart is opened the chambers contain fluid and clotted blood. The tricuspid valve admits two fingers easily. The mitral and aortic valves admit one finger. There are no valvular changes except for a few sclerotic plaques on the mitral and aortic valves. The musculature of the left ventricle is thickened. The coronary orifices are somewhat narrowed by sclerosis but are patent. Coronal section shows the coronary vessels to be patent throughout. The aorta contains numerous pearly-white and yellowish atheromatous plaques with some evidence of linear wrinkling. There is no evidence of calcification. The esophagus is unchanged. The trachea and main arteries and main bronchi contain mucus but the mucosa is intact. The pulmonary arteries and veins, the anterior and superior venæ cavæ are all unchanged. The base of the right lung is adherent to the diaphragm. The cut surfaces of the right lung are pink in color and somewhat bloody. There is no evidence of pneumonic consolidation. There is a stellate fibrous scar in the apex of the right lobe. The left is similar to the right. The right adrenal is unchanged. There is a small amount of fatty tissue surrounding the right kidney which is slightly adherent to the capsule. The capsule of the right kidney strips readily, leaving a smooth, somewhat nodular surface beneath. The cut surfaces pout on approximation. The normal markings are somewhat distorted. There is a decrease in the cortex and an increased amount of fat in the pelvis. The fatty tissue around the kidneys is gelatinous and rich in fluid. The vessels of the kidney are prominent when cut

across. The left kidney is similar to the right. The wall of the gall bladder is somewhat thickened, raised, white in color and contains yellowish bile. The common duct, portal vein and its tributaries are unchanged. The capsule of the liver is smooth, with a slight increase in the fibrous elements. The liver cuts with increased resistance. The cut surfaces show slight mottling. The cut surfaces of the spleen are dark red in color. The pulp scrapes away easily, leaving the Malpighian corpuscles and an increased amount of connective tissue standing out prominently. Grossly the pancreas is unchanged. When the stomach is opened there is a small amount of undigested food material found. The mucosa is covered with a thick layer of grayish mucous material. The mucosa is bright red in color and densely studded with petechial hemorrhages. When the large bowel is opened the mucosa is markedly hyperemic and congested. This also extends into the ileum. The prostate is not increased in size.

When the calvarium is removed the dura is thickened and the pia arachnoid stands high above the convolutions with fluid beneath. When the brain is removed all the cranial fossæ are filled with a yellowish fluid. In several areas over the vertex the pia arachnoid shows small stellate scars. Sectioning the brain shows the ventricles to be filled with fluid. The choroid plexus is intact. There are no areas of hemorrhage or softening. There are, however, petechial hemorrhages in the medullary portion. The blood is a cherry-red color.

Anatomic Diagnosis. Marked edema of the brain; dilatation of the right heart; congestion of the lungs; marked hyperemia and congestion of the mucosa of the colon and part of the ileum; marked congestion of the mucosa of the stomach; chronic diffuse nephritis; cloudy swelling of parenchymatous organs; chronic obliterative fibrous pleuritis, bilateral; fibrous splenitis; marked contractures of the hands; swelling of the knee joints.

Summary. Death appears to be the result of an overwhelming toxemia.

Pharmacologic Report. Samples of the two preparations used in our treatment of the above cases were submitted to Dr. Harold B. Meyers, Professor of Pharmacology, Department of Medicine, University of Oregon, for analysis. His results are expressed in the following communication:

"We wish to acknowledge receipt of the two preparations of ammonium ortho-iodoxy-benzoate hereinafter referred to as preparation 'A' and preparation 'B,' the latter having caused the toxic reactions described by you.

"The hydrogen-ion concentrations of 1 per cent solutions of both salts shows that preparation 'B' has a pH of 5.35 and preparation 'A' a pH of 5.75. The slightly greater acidity of preparation 'B' might play some part in the toxic reaction. It is unlikely that the difference in hydrogen-ion concentration would account for more than a minor part of the difference in toxicity of the two preparations; considering that 1 gram was the total amount of drug injected, and that it was given slowly as 1 per cent solution.

"Experimental animals injected intravenously with 1 per cent solutions of preparations 'A' and 'B' in isotonic saline with buffer salts to equalize difference in hydrogen-ion concentrations, show that preparation 'B' has a much more pronounced toxic effect than

preparation 'A.' These salts were injected in 1 per cent solution at the rate advised for human administration in dosage of 14.3 mg. per kilo, which is the concentration for an adult of approximately 150 pounds' weight. The animal injected with preparation 'B' stopped breathing, lay apparently lifeless and had very feeble heart action for some time following injection. Symptoms indicating possible fatal results occurred before the injection was completed.

"Some have asked if the iodin content of the salt might account for the toxic reaction. It is improbable that the iodin liberated as iodin from the salt could account for the toxic results because the minimal fatal dose of iodin is larger than the total amount of iodin contained in the salt. It is my belief that the toxicity is due probably to an intermediary substance prepared in the process of manufacture, such as an iodoso compound, which is relatively highly toxic."

Summary. Five cases of different types of arthritis were treated with two brands of ammonium ortho-iodoxy-benzoate intravenously. With the first preparation, oxoate, 10 injections were given with some, alleviation of symptoms and no untoward results. One injection of a second preparation given to each of 3 of these cases previously treated produced severe toxic symptom in 2 and death in the third. A fourth individual suffering from gonorrheal arthritis who had had no previous injections was given one dose of the second preparation with toxic reaction.

Conclusions. Our clinical experience with these four simultaneous reactions speaks against the assumption that an individual idiosyncrasy either to iodin or salicylates is probable. Furthermore, animal experimentation with two different preparations showed a difference in toxicity. The technique of administration was identical in each instance. It has been suggested and is, in our opinion, quite likely that, either in manufacture, administration or decomposition of the drug in the blood stream, there was set free an intermediary toxic product which was responsible for the injurious effects observed.

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INOCULATION MALARIA: SEXUAL AND ASEXUAL STRAINS.

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The practical value of an asexual strain of malaria in the treatment of general paralysis as has already been pointed out, lies in the fact that "(*a*) it eliminates the possibility of the transmission of malaria to other members of the community; (*b*) it precludes the occurrence of malarial relapse following adequate quinin administration."[1] In a single strain of benign tertian malaria continuously in use since June, 1923, in over 350 patients we have so far failed to find any gametocytes in peripheral blood smears.

The question immediately arises as to whether a sexual strain of benign tertian malaria would lose its capacity to develop gametocytes upon continuous artificial human passage. The present report deals with this problem.

A strain of malaria was obtained in which gametocytes were present.* This strain was first used on May 9, 1928 and up to August 8, 1929, 123 patients have been inoculated—88 females and 35 males. As a rule such inoculations were made intravenously, occasionally subcutaneously. The malarial course paralleled that induced by our former "asexual"† strain and the therapeutic results in general paralysis were identical.

Daily smears from all patients were examined from the first elevation of temperature to its cessation. In all, over 1700 Wright-stained slides were studied microscopically.

In general most of the slides contained malarial parasites (in varying numbers). The important point under consideration is the comparative presence and absence of gametocytes.

A striking difference is to be noted between the two groups as regards the per cent of slides with parasites showing gametocytes. In order to bring this point out more clearly, averages are presented in Table I.

TABLE I.—GAMETOCYTES IN FEMALE PATIENTS.

	Average per cent of slides with parasites showing gametocytes.	Actual number of cases showing no gametocytes.
Group 1—Case Nos. 1 to 44 . . . . . (May 9 to November 2, 1928.)	69	0
Group 2—Case Nos. 45 to 89 . . . . . (November 2, 1928 to August 8, 1929.)	16	13
Reduction	53	

* Thanks are due Dr. C. O. Cheney, Superintendent of the Hudson River State Hospital, Poughkeepsie, N. Y., for his kind coöperation in securing this strain.

† Asexuality will have to be finally determined by testing transmission by mosquitos.

Table I is arbitrarily divided into two equal groups: Case Nos. 1 to 44 constituting the first group and Case Nos. 45 to 88 constituting the second group. In point of time the first group was inoculated during a period of seven months. The second group was inoculated during the succeeding nine months.

Thus, compared with the first group there has been a reduction in the second group of 53 per cent in the average per cent of slides with parasites showing gametocytes. Furthermore, in the first group of 44 patients there was not a single patient whose slides showed parasites with a complete absence of gametocytes. Contrast this with the second group of 44 patients where there were 13 patients whose slides with parasites contained absolutely no gametocytes. In other words, gametocytes failed to appear in approximately one-third of the patients in the second group.

These findings point definitely to the fact that in female patients the sexual strain of malaria is rapidly losing its capacity to produce sexual forms. How many more passages will be required before the sexual strain becomes entirely asexual is a matter of speculation but the investigation is being continued. Again it should be emphasized that clinically no differences could be observed between patients having sexual forms of the malarial parasite and those having only asexual forms.

Consider now the results obtained with male patients. These are presented in Table II where an arbitrary division has been made on approximately the same time basis as in the female patients, that is, all male patients, Case Nos. 101 to 114 inoculated during the first seven months fall in the first group, while Case Nos. 115 to 135 fall in the second group during the subsequent nine months.

TABLE II.—GAMETOCYTES IN MALE PATIENTS.

	Average per cent of slides with parasites showing gametocytes.	Actual number of cases showing no gametocytes.
Group 1—Case Nos. 101 to 114 (May 9 to October 23, 1928.)	73	0
Group 2—Case Nos. 115 to 135 (November 9, 1928 to August 3, 1929.)	38	1
Reduction	35	

From Table II it will be seen that in the first group 73 per cent of patients having slides with parasites showed the presence of gametocytes, while in the second group the corresponding figure was 38 per cent. This represents a reduction of 35 per cent. It will be remembered that in female patients the reduction for the same period of time was greater, namely, 50 per cent. No patient in the first male group and only one patient in the second male group had a total absence of gametocytes when malarial parasites were present. Again it will be recalled that 13 female patients or approximately one-third of the second group had a total absence of gametocytes.

The obvious inference from these findings is that while there is some tendency for the sexual strain to lose its capacity to produce gametocytes in male patients, this tendency is not nearly so striking as in female patients. Human sex differences apparently exert an unmistakable influence upon the life cycle of the malarial parasite. An adequate explanation of this curious phenomenon is still wanting.

It was stated at the outset that the "asexual" strain of malaria is still being used therapeutically. During the progress of the present investigation the inoculation of the 88 female and 35 male patients with a sexual strain of malaria was paralleled by the inoculation of 36 patients with our older "asexual" strain of malaria. Daily examination of all stained smears in the latter patients failed at any time to reveal the presence of gametocytes. This corroborates our previous findings.[1]

Biologically it appears, then, that a sexual strain of malaria upon repeated human passage loses its capacity to produce sexual forms. Such an adaptation might well be anticipated in the light of our knowledge of parasitism. The malarial parasite must have sexual forms to complete its life cycle in mosquitos but gametocytes are unnecessary for further propagation in *homo sapiens* exclusively. Clinically this biological adaptation possesses certain advantages to which reference has already been made.[1]

Therapeutically there is practically no difference between the "asexual" and sexual strains of malaria. Thus Hinsie[2] working at the Psychiatric Institute, found that 32 per cent of female patients with general paralysis showed improvement when inoculated with the "asexual" strain of malaria. In the series of cases here described many female patients were nonluetic but among the general paralytics 27 per cent showed improvement when inoculated with the sexual strain of malaria. Again in male general paralytics, Bunker and Kirby[3] found that 55 per cent improved when inoculated with the "asexual" strain of malaria, while in our series of male general paralytics 54 per cent improved when inoculated with the sexual strain of malaria. Obviously the slight discrepancy in favor of the "asexual" strain falls well within experimental error and the conclusion remains that sexual and "asexual" strains of malaria follow the same clinical course.

Summary. 1. The malarial course and therapeutic results in 123 patients (88 females and 35 males) inoculated with a sexual strain were identical with those noted in over 350 patients inoculated with an "asexual" strain of malaria.

2. After seven months the sexual strain of malaria began to lose its capacity to produce gametocytes. During the succeeding nine months this was found to be much more striking in female than in male patients. Approximately one-third of all the female patients having malarial parasites failed to reveal the presence of any sexual forms of the plasmodium.

3. The sexual strain of malaria becomes biologically adapted to its host upon repeated human passage, as evidenced by its increasing failure to produce gametocytes.

NOTE.—Particular acknowledgment is due Mr. Peter Cohen for his active assistance in this investigation. It is always a privilege to express appreciation of the interest and coöperation of Dr. George H. Kirby, Director of the New York State Psychiatric Institute and Hospital, the present members of the Clinical Staff, Drs. L. E. Hinsie and Joseph R. Blalock, and the former members, Drs. C. O. Fiertz and Samuel Parker.

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THE INCIDENCE OF PRIMARY CARCINOMA OF THE LUNG.

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IN 1912, after an extensive review of the literature, Adler[1] collected 374 cases of carcinoma of the lung. He noted then, that "on one point however, there is nearly complete consensus of opinion, and that is that primary malignant neoplasms of the lungs are among the rarest forms of disease." Since then there has appeared a considerable literature attesting to the increased frequency of this condition. The etiologic, clinical and pathologic aspects of primary carcinoma of the lung have received adequate attention, but not enough emphasis has been placed on the question of incidence. This paper will attempt to correlate evidence pertaining to the frequency of primary carcinoma of the lung, and to present new evidence from the Boston City Hospital.

Some idea of the more frequent occurrence of primary carcinoma of the lung today, may be gained by comparing the older reports with those of the present. Reinhard[2] collected 5 cases among 8716 autopsies in Dresden from 1852 to 1876, and Fuchs[3] found 8 cases among 12,307 autopsies in Munich from 1854 to 1885. More recently, Symmers,[4] at Bellevue Hospital, saw 8 cases from July, 1919, to December, 1920; and Moses[5] reported 3 cases occurring between February 12 and June 1, 1924, at the Kings County Hospital. Ferenczy and Matolcsy,[6] in a review of the autopsy material at the Pathological Institute, Vienna, found only one case in 1896, and 32 cases in 1924. From 1910 to 1918 there were 4 cases of primary

carcinoma of the lung at the Boston City Hospital among 964 adult autopsies (0.42 per cent), and this increased in the years 1919 to 1928 to 17 cases among 2040 autopsies (0.83 per cent).

For valid comparison of the incidence of this condition definite criteria for diagnosis and statistical report should be established. Of these, the following have been modified from Weller:[7]

1. An autopsy must have been performed.
2. The carcinomatous nature must have been verified microscopically.
3. There must be no reasonable doubt that the neoplasm was not a primary growth.
4. Percentage should be calculated on the basis of total adult necropsies.

Although gross section is often sufficient for a pathologic diagnosis of primary carcinoma of the lung, in an occasional instance histologic examination is necessary to differentiate other noncarcinomatous intrathoracic neoplasms—lymphosarcoma, fibrosarcoma, lymphoblastoma. Where there is no microscopic examination, it may be reasonable to believe that the condition is not carcinoma, and these cases should not be included in statistical reports. Also, the primary lesion is frequently allocated to the lung in many instances in which that organ is involved in a generalized carcinomatosis. For accurate statistical data, if there is any reasonable suspicion that the primary growth was not in the lung, the case should be excluded. It is evident also, that the percentage incidence will be effected by the age group of patients undergoing autopsy examination. In a general hospital, with a large active pediatric service, where in the autopsy material there is fair representation of the noncarcinomatous age group, the incidence if based on total autopsies, will be lower than in a hospital with few pediatric cases. For purposes of comparison, therefore, a uniform method of arriving at percentage incidence should be established. In the author's series, following the example of Berblinger[8] and Wahl,[9] the percentage incidence is based on the number of autopsies of patients over twenty years of age, twenty being taken arbitrarily as the lowest age limit of carcinoma.

The major statistical studies of primary carcinoma of the lung have been made on the Continent. Only a few have appeared in the English and American journals. Although with one or two exceptions all authors are convinced that this affection is more frequent now than it was a generation ago, a satisfactory comparison of the percentage incidence from the statistics cited presents many difficulties. Some authors include all intrathoracic new growths; others only carcinomas. Some authors form percentage figures on the basis of total necropsies, irrespective of age; others on total adult autopsies, that is, patients over twenty years of age. Some groups are too small to permit satisfactory conclusions; in others,

insufficient data are given; and in a few reports histologic examination has not been performed or no statement is made that it has been performed.

TABLE I.—A SUMMATION OF THE INCIDENCE OF PRIMARY CARCINOMA OF THE LUNG, AS GIVEN BY VARIOUS AUTHORS.*

Year.	Summated from authors who give total autopsies, total number of all cancers and total primary lung cancers.			Summated from authors who give total number of autopsies and total number of lung cancers.			Summated from authors who give total number of all cancers and total number of lung cancers.		
	Total autopsies.	Total cancers.	Total cancers to total autopsies, per cent.	Total autopsies.	Total lung cancers.	Total lung cancers to total autopsies, per cent.	Total cancers.	Total lung cancers.	Total lung cancers to total cancers, per cent.
To 1899	27,126	2201	8.11	63,633	89	0.14	2201	32	1.45
1900-1904	16,523	1379	8.34	21,818	45	0.21	1614	41	2.54
1905-1909	22,862	2360	10.32	27,268	95	0.35	2595	91	3.50
1910-1914	31,229	3246	10.39	37,580	165	0.44	3560	161	4.52
1915-1919	43,524	4437	10.19	49,244	213	0.43	4857	209	4.30
1920-1924	38,458	4788	12.47	43,379	354	0.81	5204	344	6.61
1925-1928	6,929	1069	15.43	6,929	94	1.36	1069	94	8.79
1910-1919	74,753	7683	10.27	86,824	378	0.44	8417	370	4.39
1920-1928	45,387	5857	12.90	50,308	448	0.89	6273	438	6.98

* Some investigators omit the total number of autopsies, others do not give the total number of cancers. This incompleteness necessitates the tabular form presented.

Recognizing these sources of error in computing a satisfactory comparative incidence, Table I was constructed. It represents a summation of the reports of Berblinger,[8] Breckwoldt,[10] Fuchs,[3] Hanf,[11] Holzer,[12] Katz,[13] Kikuth,[14] McCrae,[15] Marchesani,[16] Materna,[17] Moise,[18] Pässler,[19] Reinhard,[2] Sonnenfeld,[20] Staehelin,[21] Wahl,[9] Wolf[22] and the author's series from the Boston City Hospital. The reports of Bonser,[23] Duguid[24] and Simpson,[25] were not included since these authors considered all intrathoracic tumors. The data of Seyfarth[26] were excluded because of incompleteness. Last were excluded the statistics (Table II) of Barron,[27] Biberfeld,[28] Brandt,[29] Briese,[30] Eichengrün and Esser,[31] Ferenczy and Matolcsy,[6] Fried,[32] Grove and Kramer,[33] Klotz,[34] Lavrinovich[35] and von Wiczkowski,[36] because they do not give yearly frequency or because they could not be represented conveniently in the year groups of Table I. With the exception of Bonser, however, all of the authors whose work has not been included in Table I, recognize an increase in lung cancer. This table shows a steady rise in the relation of primary carcinoma of the lung to total autopsies and to all carcinomas.

TABLE II.—THE INCIDENCE OF PRIMARY CARCINOMA OF THE LUNG.*

Author.	Year.	Total autopsies.	Cancers.		Primary lung cancers.		
			Total No.	Autopsies, per cent.	Total No.	Autopsies, per cent.	All cancers, per cent.
Barron . .	1899–1911	1,332	...	...	0		
Briese . .	1898–1916	12,971	1287	9.92	60	0.46	4.7
Wiczkowski .	To 1913	58,497	...	...	125	0.21	
Lavrinovich .	1905–1915	16,047	1649	10.28	61	0.38	3.7
Klotz . . .	1910–1920	1,000	...	...	5	0.50	
Ferenczy and Matolcsy .	1896–1925	62,802	6791	10.80	282	0.45	4.1
Biberfeld . .	1897–1925	36,428	...	...	207	0.57	
Barron . .	1912–1918	2,026	...	...	4	0.19	
Barron . .	1919–1921	1,003	...	...	9	0.89	
Brandt . .	1901–1925	13,179	1825	13.83	108	0.82	5.9
Eichengrün and Esser .	1902–1926	13,318	932	7.07	68	0.51	7.3
Fried . . .	1915–1925	1,400	136	9.71	5	0.35	3.6
Grove and Kramer .	1917–1924	3,659	...	...	21	0.57	
Klotz . . .	1920–1927	1,900	...	...	19	1.00	

* These statistics are not included in Table I.

Reports from the Dresden City Hospital are available which give the incidence over a period of fifty years (Table III).

TABLE III.—PRIMARY CARCINOMA OF THE LUNG AT THE DRESDEN CITY HOSPITAL.

Author.	Year.	Total autopsies.	Autopsies which were lung cancers, per cent.	All cancers which were lung cancers, per cent.
Reinhard[3] . .	1852–1876	8,716	0.057	0.92
Wolf[22]	1877–1894	11,400	0.351	
Rau[37]	1909–1914	4,905	0.306	2.72
	1914–1919	5,488	0.490	4.66

The relation of primary carcinoma of the lung to all cancers rose from 0.9 to 4.66 per cent in the years 1852 to 1919, a considerable increase.

In England, Rolleston and Trevor[38] reviewing 3983 autopsies at St. George's Hospital from January 1, 1890, to July 8, 1902, found 8 instances of neoplasm of the lung, of which only 2 were carcinomas. A similar low incidence is reported by Playfair and Wakeley[39] from King's College Hospital. Among 3183 autopsies from 1901 to 1923, there were only 4 cases of primary carcinoma of the lung in which there was no element of doubt in the diagnosis, an incidence of 0.1 per cent. More recently statistics from England have been very much higher, among the highest in the literature, probably

because all intrathoracic new growths are included in the surveys. Duguid[24] and Simpson[25] have each noted a substantial increase in intrathoracic malignancy, and each is satisfied that there is a true increase in carcinoma of the lung. Moreover, Simpson's figures from the London Hospital indicate that there was no associated increase in the total carcinomas from all parts of the body.

Bonser's analysis of autopsied cases at the Leed's General Infirmary during the years 1891–1927 showed no increase in intrathoracic cancer, and this in a hospital where 83.6 per cent of all deaths in thirty-seven years have undergone autopsy examination. However, of the 172 cases of intrathoracic malignancy which Bonser found, only 60 cases or 35 per cent were examined histologically. Of these 60 cases, 24 were oat-cell sarcoma of the mediastinum, 6 were small round-cell sarcomas, and 2 were Hodgkin's sarcoma. It is conceivable that the yearly distribution of the noncarcinomatous intrathoracic neoplasms in Bonser's series obscures an actual increase in the frequency of true carcinoma.

Both Bonser and Simpson are of the opinion that intrathoracic new growths are usually carcinomatous. Simpson states that Turnbull "has for many years held the view that primary malignant disease of the lungs and bronchi are nearly all carcinomata, and that the so-called 'oat-celled sarcomata' (also termed lymphosarcomata, mediastinal sarcomata, lymphosarcomata of the mediastinum) are in reality true carcinomata." Barnard[40] also concludes that the oat-cell sarcoma of the posterior mediastinum is a medullary carcinoma of the bronchus. Nevertheless, until this view is generally accepted, it is well to include in a study of carcinoma of the lung, only those conditions which are universally recognized as carcinomatous.

In spite of the rather widespread belief that primary carcinoma of the lung is a rare condition, in the author's series of 314 cancer deaths, the lung stands fifth in the order of involvement. Kikuth,[14] studying postmortem sections at the Hamburg Eppendorf Hospital in 1923, found that the lung was the organ second most frequently affected by carcinoma. A similar study by Eichengrün and Esser[31] of 932 cancer deaths or 7 per cent of all autopsies from 1902 to 1926, placed carcinoma of the lung fifth in frequency, and Briese,[30] studying 1287 cancer cases comprising 10 per cent of autopsies from 1898 to 1916, found it the sixth most frequent cancer.

In reviewing the autopsy protocols at the Boston City Hospital the criteria previously noted were rigidly adhered to. The reports are full and complete, and all cases have had microscopic examination. Moreover, there has been no change in the supervisory staff. Dr. Frank B. Mallory, to whom the author is indebted for the use of this material, has been in active charge of the Department of Pathology during the entire period considered. In doubtful cases the histologic sections were reëxamined.

From 1910 to 1928 there were 3004 adult autopsies, of which 314 or

10.4 per cent were cancer cases. Primary carcinoma of the lung occurred twenty-one times or 0.70 per cent of all adult autopsies, and 6.69 per cent of all cancers (Table IV). Other intrathoracic tumors observed were three fibrosarcomas, one endothelioblastoma, and one mesothelioma. Lymphoblastomas were not included. In the period 1925 to 1928, the percentage relation of all cancers to total autopsies increased from 10.29 to 12.35 (an increase of 20 per cent). Coincidentally, the percentage relation of primary carcinoma of the lung to total autopsies rose from 0.57 to 1.03 (an increase of 81 per cent); and the percentage relation of primary carcinoma of the lung to all cancers rose from 5.55 to 8.28 (an increase of 49 per cent). The increase in primary carcinoma of the lung is evidently much greater than the increase in all cancers. The group is of course too small to indicate an absolute increase in lung carcinoma, but the results are highly suggestive of a real rise in incidence.

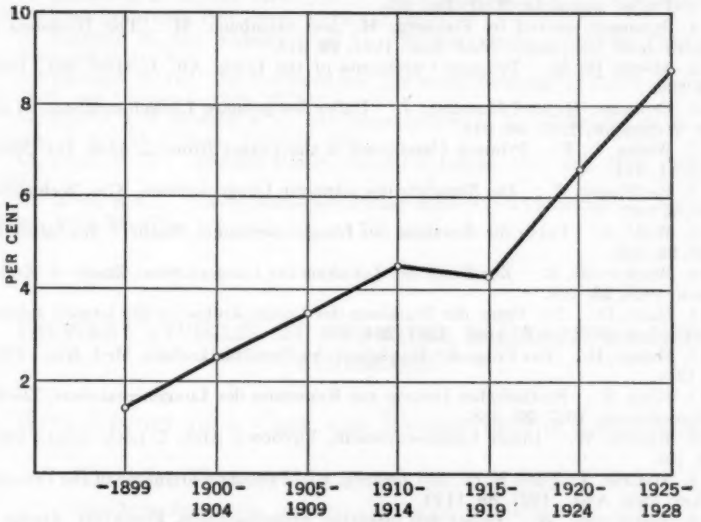
TABLE IV.—PRIMARY CARCINOMA OF THE LUNG AT THE BOSTON CITY HOSPITAL.

Year.	Number of adult autopsies.	Carcinomas.		Primary lung carcinomas.		
		Total number.	Autopsies, per cent.	Total number.	Autopsies, per cent.	All carcinomas, per cent.
1910–1914 . .	438	34	7.76	2	0.46	5.88
1915–1919 . .	526	45	8.55	2	0.38	4.44
1920–1924 . .	874	90	10.29	5	0.57	5.55
1925–1928 . .	1166	145	12.35	12	1.03	8.28
1910–1928 . .	3004	314	10.45	21	0.70	6.69

There is evidently much difference of opinion over the question whether this increase, noted by practically all observers, is a real, absolute increase, peculiar to the lung, or only relative to and coincidental with a general increase in systemic cancer. Simpson,[25] Duguid,[24] Wahl,[9] and Rau,[37] are convinced that this increase is a real one, while Lichty,[41] Eichengrün and Esser,[31] Fried,[42] and Marchesani[16] feel that the greater frequency is only relative and associated with an increase in carcinoma cases. If the increase in primary carcinoma of the lung were due to the increase in all cancers, then over a period of years the relationship between these two factors would be constant, and the curve showing the percentage relation of lung cancers to all cancers would be represented by a horizontal line. That this is not so is shown by the graph (Chart I) drawn from the statistics in Table I. The trend of the curve is definitely up. This chart does not involve the age group of autopsy material since only carcinomas are considered, and so one source of error, infant autopsies, is eliminated. The conclusion must be drawn that in recent years there has been a real, absolute increase in the frequency of primary carcinoma of the lung.

Certain factors have been presented which might contribute

towards this increase. That clinical and pathologic acumen is greater today than it was a generation ago cannot be doubted. More cases are diagnosed both pre- and postmortem. Also, as Wells[43] rightly observes, the tremendous advances in communication and modes of transportation make modern diagnostic facilities available to the most secluded hamlet. As a result, more and more patients with bizarre symptoms come to hospitals for observation, and especially for roentgenologic examination. Then too, in hospitals where interns secure permission for necropsy, greater efforts are made to obtain consent for the examination of interesting



The percentage relation of primary carcinoma of the lung to all carcinomas. Drawn from the statistics in Table I.

cases. But there seems to be no reason why these considerations should be effective only with regard to carcinoma of the lung. They apply with equal force to carcinoma of any organ, and for that matter to any puzzling disease that presents diagnostic difficulties. If these factors alter the postmortem frequency of carcinoma of the lung, they will alter to the same degree the postmortem frequency of all cancers, and the percentage relationship therefore, will not be influenced.

Conclusions. 1. The postmortem incidence of primary carcinoma of the lung is steadily increasing, and this increase is real and absolute.

2. Combined statistics show that primary carcinoma of the lung at autopsy from 1910 to 1919 comprised 0.44 per cent of autopsies, and 4.39 per cent of all cancers. Since 1920, primary carcinoma of the lung at autopsy comprised 0.89 per cent of autopsies and 6.98 per cent of all cancers.

3. Primary carcinoma of the lung is not as rare as was formerly believed. Because of its increased frequency, the clinician should give this affection serious consideration in differential diagnosis in patients of the carcinomatous age presenting puzzling lung symptoms and signs. An early diagnosis will permit accurate prognosis, and in selected cases, perhaps, surgical therapy.

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TERTIARY SYPHILIS OF THE LIVER SIMULATING BANTI'S SYNDROME.

With Report of a Case and Review of the Literature.

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The question of whether the clinical-pathologic complex described some thirty-five years ago by Banti is really founded upon pathologic changes peculiar to itself, and is thus entitled to the designation "Banti's disease," or whether it is simply a superficial variant, or result, of some separate and distinct pathologic entity, and therefore merits a status no more definite than that of a syndrome, remains unanswered. A further problem, or perhaps the primary problem, concerns the etiology of this syndrome, about which there is no agreement whatsoever. At one extreme we have Banti's original assertion that it is a disease *sui generis*, and at the other the declaration of Norris, Symmers and Shapiro[114] that the syndrome is nothing more than one of the manifestations of tertiary syphilis. The interjacent territory is occupied by those—for example, Neuberg[56]—who believe that any one of many infectious or "toxic" agents, operating in the portal system, may reproduce all the essential clinical and pathologic manifestations of the Banti syndrome.

It is not the intent of this paper to enter into this controversy, nor to recite its pros and cons. For a comprehensive discussion of the problem the reader is referred to the papers of Wentworth,[124] who brings the subject up to 1901 and appends a long bibliography, Stein,[121] Leon-Kindberg,[43] whose bibliography contains 135 references, Krull,[41] Moschcowitz,[110] and Carr.[89] Moschcowitz's critique, in particular, is penetrating and illuminating. Suffice it for our purpose to say that even the most casual examination of the literature leads to the conviction that the syndrome often appears to manifest itself *ab initio* as an independent process, whereas not infrequently it is found to be reproduced perfectly by tertiary syphilis of the liver. If it has other apparent origins they are not of sufficiently frequent occurrence, or sufficiently unequivocal, to demand serious attention. Certain it is that in the present state of our knowledge it would be better to let the question of etiology remain *sub judice*, employing meanwhile the designation "Banti's syndrome" in preference to "Banti's disease."

Ex cathedra pronouncements, such as that of Norris, Symmers and Shapiro,[114] that Banti's syndrome is always caused by syphilis, serve chiefly to obfuscate the problem. Those who take the trouble to look will find in the records a great many cases of Banti's syndrome in which it was established beyond reasonable doubt that syphilis played no part whatsoever in the etiology. The authors would have done well to mend their own fences; they forget that the clinical aspects of Banti's syndrome demand some attention. The statement of Symmers, Gettler and Johnson[76] that their 6 cases, or at least 3 of them (which 3 not indicated), were diagnosed clinically as Banti's syndrome, would carry more conviction if the cases had been described in sufficient detail to enable the reader to form his own opinion (see Tables II and III, and discussion).

It is the purpose of this paper to report a case of tertiary syphilis of the liver which manifested itself as Banti's syndrome in the terminal stages, and to collect from the literature as many similar cases as possible. As far as I can discover, a comprehensive review and critical analysis of these cases from this point of view has never been published.

Report of Case. *History.*—The patient was born in 1901 and was considered a perfectly healthy and robust child until 1912, at which time she suffered a severe attack of scarlet fever. Thereafter, she never regained her former vigor and good health. She remembered being told by her school teacher that her color was "bad." In 1915 she had measles, recovery from which was interrupted by an upper respiratory infection with fever, following exposure to cold and wet. After this she was neither better nor worse, but remained in a state of chronic ill-health characterized by weakness, secondary anemia, and intermittent attacks of very mild jaundice. The last-named symptom made its first appearance shortly after her scarlet fever. The patient did not begin to menstruate until she was twenty years of age, and never had more than three menstrual periods a year, always with scanty flow.

Throughout the summer of 1924 the patient had an almost continuous fever of unknown origin, reaching frequently as high as 103° F. She felt unusually weak and "nervous" during this period, but there were no definite localizing symptoms. In the fall of 1924 she was examined by a physician who told her that she had an enlarged spleen, and she remembered that for a year or more prior to that time she had noticed soreness in the splenic region intermittently, especially after exertion. This symptom continued without change throughout the rest of her illness. Some time in the winter of 1924–1925 a dull ache appeared in the right leg and thigh, increasing gradually in intensity until it interfered with sleep. Two weeks later a similar ache made its appearance in the left arm, and increased slowly. Because these aching pains were never aggravated by movement of the joints the patient felt that they originated in the bones themselves. Finally they spread to most of the long bones, and although they never became extremely severe, they continued to annoy her intermittently ever afterward.

Early in September, 1928, the patient passed a tarry stool, and found herself unusually weak the next day; there was no coincidental abdominal pain. Aside from this single experience, there was no history of hemorrhage from the gastrointestinal tract.

About September 1, 1928, while holding a trivial weight in her left hand, meanwhile keeping her left arm braced against her body, she was reaching upward with her right arm when she felt and heard something snap in her left arm and immediately experienced an excruciating pain just above the left elbow. The next day the left arm was swollen and slightly warmer than its fellow, and it remained swollen and painful until she was admitted to the hospital a month later.

There was no family history of tuberculosis or jaundice. The patient's parents and two brothers were alive and well; two brothers and a sister died in infancy from unknown causes. She was married in 1922, but had never been pregnant, a circumstance which she ascribed to the fact that her uterus was "underdeveloped." She denied venereal infection.

Physical Examination. Patient was admitted to the University Hospital, September 27, 1928, complaining of pain in the left arm, and general weakness. She was a poorly nourished, fragile little woman, aged twenty-seven years, pale and slightly jaundiced. The left arm, elbow and upper fore-arm were much swollen. The shoulder and elbow joints were unaffected, but just proximal to the elbow there was an area of extreme tenderness, and all attempts at active or passive movement of the arm resulted in excruciating pain in this area.

There was a normal growth of hair on the head, in the axillæ, and over the pubes. The skull was not remarkable. The nose was normal. Hearing and vision were unimpaired. The scleræ were slightly icteric. The corneæ were absolutely clear, the pupils reacted satisfactorily to light and in accommodation, and the fundi were negative to ophthalmoscopic examination. All the teeth had been removed. The tongue, pharynx and tonsils were not abnormal. A few lymph nodes were palpable in the cervical, inguinal, and femoral groups, but the character and extent of the enlargement were insignificant.

Examination of the lungs showed nothing except a few râles and a small amount of fluid at both bases. The heart was moderately dilated; the peripheral arterial pulse was not of large volume, but was distinctly celer in character; and there was an endocardial (hemic) systolic murmur over the conus arteriosus—changes which were quite in keeping with the long-standing anemia. There were no signs of disease of the aorta. The arterial blood pressure was 106/56 mm. Hg.

The abdomen was somewhat enlarged, and a few slightly dilated veins were visible along either side. There was a moderate amount of ascites.

The spleen was greatly enlarged, reaching to the level of the umbilicus and extending several centimeters to the right of the midline; its surface was smooth, its consistency firm, and its edge moderately rounded; it was slightly tender to pressure. The liver was not only not enlarged, but distinctly smaller than normal, so that none of its physical characters could be made out.

There was some edema below the knees, none elsewhere. No abnormal neurological signs were discovered. Vaginal examination revealed a small nulliparous uterus, but no definite abnormalities.

Laboratory Examination. The initial blood cell counts showed 3,250,000 erythrocytes; and 6200 leukocytes, of which 76 per cent were polymorphonuclear neutrophils, and 20 per cent lymphocytes. The blood Wassermann reaction was strongly positive. The resistance of the erythrocytes to hemolysis by hypotonic salt solution was greatly increased (hemolysis began at 0.34 per cent and was complete at 0.22 per cent). The blood platelets were diminished in number, the reticulocytes slightly increased, and the bleeding time and coagulation time normal. The presence of bilirubinemia was proved by a positive van den Bergh reaction. The urine was normal except for the presence of small amounts of bilirubin and bile salts, proving that the jaundice was obstructive.

Roentgenograms showed a destructive lesion and pathologic fracture of the left humerus (Fig. 1); a diffuse, sclerotic lesion, with periosteal proliferation, involving the left tibia, left fibula, and right tibia; destructive and sclerotic lesions, with periosteal proliferation, of both femora, especially the right; and a destructive process involving the right humerus. It was the roentgenologist's opinion that these lesions were syphilitic in nature.

Summary. History of anemia, intermittent slight jaundice, and splenomegaly, all of many years' duration, beginning early in life. History of sterility. Presence of mild obstructive jaundice, shrunken liver, splenomegaly, ascites, secondary anemia, leukopenia, diminished fragility of erythrocytes, widespread syphilitic lesions of the long bones, and a strongly positive blood Wassermann reaction; to these should be added slight melena and profuse epistaxis and hematemesis which supervened during patient's residence in the hospital.

Diagnosis. Tertiary syphilis (congenital?) of the liver and spleen, reproducing the clinical features of Banti's syndrome; syphilitic osteosclerosis, periostitis and caries of long bones; pathological fracture of the left humerus.

Subsequent Course. At first there was a slight remittent fever, never exceeding 101° F., which disappeared after ten days, not to return. The icterus was variable in degree, sometimes being absent entirely.

The steady accumulation of ascitic fluid necessitated three paracenteses (October 13, November 7, November 28, giving issue to 3000 cc., 3000 cc. and 5500 cc., respectively); the fluid was clear, greenish-yellow in color, of low specific gravity, contained from 8 to 13 gm. of albumin to the liter, contained no bile pigment or blood, and at first gave a strongly positive Wassermann reaction. The Wassermann on the fluid removed November 28, after the antisyphilitic treatment had begun to take effect, was only slightly positive.

The following antisyphilitic treatment was given: Potassium iodid by mouth, in daily doses of 1 gm.; potassium-bismuth-tartrate intramuscularly, in weekly doses of 0.1 or 0.2 gm., over a period of nine weeks (total 1.1 gm.); and, during the latter part of the period of bismuth administration, neoarsphenamin intravenously, in weekly doses of 0.2 or 0.3 gm. (total 1.4 gm.). The blood Wassermann reaction continued to be strongly positive after four weeks of treatment. The net result of this therapy was a 30 or 40 per cent reduction in the volume of the spleen, and complete healing

FIG. 1

FIG. 2

FIG. 3

FIG. 1.—Left humerus. Roentgenogram taken before starting antisyphilitic treatment, showing extensive syphilitic osteolysis and pathologic fracture. The fracture was a month old at this time, but there is no indication of a reparative process.

FIG. 2.—Left humerus. Roentgenogram taken during course of antisyphilitic treatment, showing beginning of callus formation about the pathologic fracture.

FIG. 3.—Left humerus. Roentgenogram of portion removed at autopsy, showing satisfactory bony union.

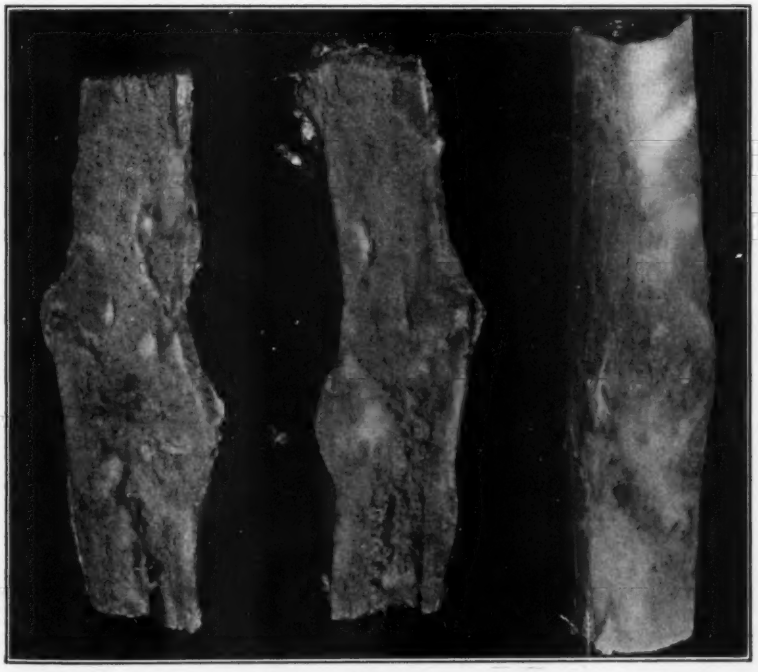

FIG. 4.—Left humerus. Photograph of portion removed at autopsy, showing complete healing of fracture.

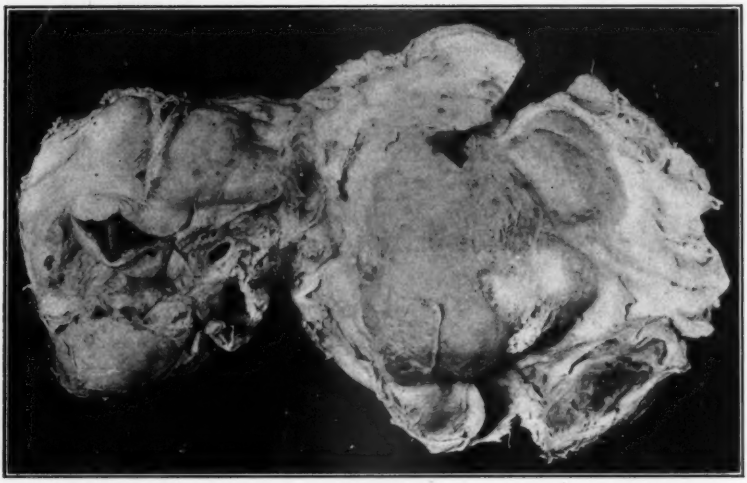

FIG. 5.—Liver. Gross appearance of postmortem specimen, showing extreme deformity, and reduction in volume of right lobe.

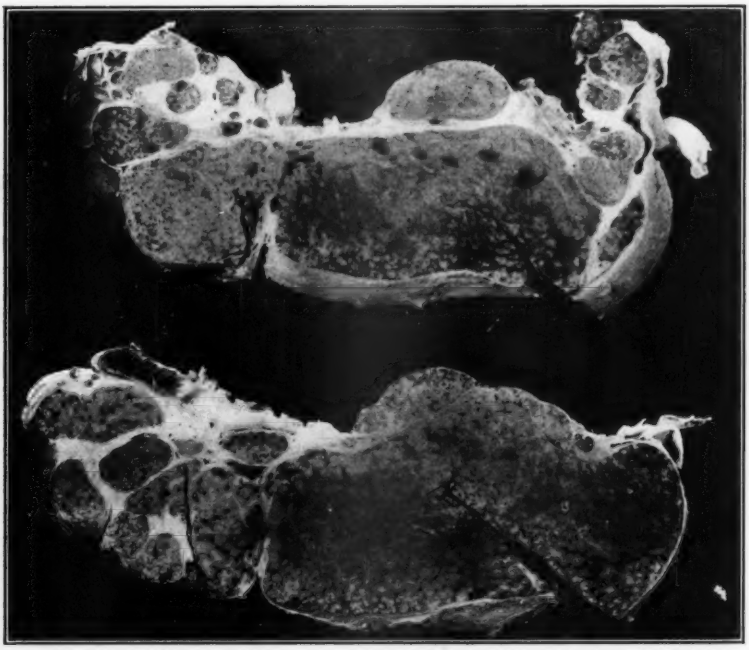

FIG. 6.—Liver. Transverse sections, showing extensive scarring, especially about the hilus and throughout the shrunken right lobe.

of the pathological fracture (Figs. 2, 3, 4, and necropsy protocol); in other respects the patient's condition grew slowly but steadily worse.

Blood examination:

	Hb., per cent.	R.B.C.	W.B.C.
Oct. 3	45	3,110,000	6850
Oct. 30	50	2,380,000	
Dec. 4	54	2,460,000	4000
Dec. 19	30	1,800,000	4650

About December 1, 1928, there were brisk and repeated epistaxes; later the epistaxis was renewed, and hematemesis occurred. Transfusion of blood was resorted to several times with temporary benefit. Patient died of hematemesis December 20, 1928.

The question of whether or not splenectomy should be performed was considered seriously, but it was thought to be inadvisable without a preliminary course of antisyphilitic treatment, and later the patient's condition rendered it too hazardous. Judging from the state of the liver as discovered at autopsy, splenectomy would not have modified the course of the illness, except perhaps unfavorably.

Necropsy Protocol (Excerpts) (Dr. G. H. Hansmann). Skin very pale; skin and scleræ questionably icteric. Numerous petechiæ and ecchymoses, especially over the lower extremities. Bloody discharge from the left nostril. Left humerus palpably thickened in its lower third, but no false motion at the site of thickening.

The left pleural cavity contained 350 cc. of bloody fluid; the right, 450 cc. of clear fluid. The inferior third of the right lung was covered as with a cap by thick, white, fibrous pleura which was extensively and firmly adherent to the chest wall, pericardium and diaphragm. The pleura at the base of the left lung was also thickened and adherent to the pericardium and diaphragm. The lungs showed no abnormalities of any consequence.

The heart and aorta showed no noteworthy changes.

The peritoneal cavity contained 1700 cc. of clear yellow fluid. The liver was removed only with the greatest difficulty because of the very dense, continuous adhesions between it and adjacent structures, particularly the diaphragm. As a whole, it presented the characteristic appearance of a *foie ficelé* (Figs. 5 and 6). Its weight was 950 gm. The right lobe was about one-fourth as large as normal, and one-third as large as the left lobe. It consisted of a group of irregularly shaped nodules measuring from ½ to 5 cm. in diameter, separated by firm, deep scars; some of these lobules of liver tissue seemed almost normal. The consistency of this lobe was somewhat softer than that of the left; the cut surface presented a dark, mottled appearance. The left lobe presented a similar mottled appearance, and contained areas of bile-stained tissue which were thought to represent regenerated liver cells. Histologic examination showed many bands of dense fibrous tissue radiating from the capsule into the liver substance; much replacement of liver tissue by localized areas of scarring; some regeneration of liver cells in rounded lobules in which the normal architecture of the liver cords was disturbed; much stasis of bile; and no acute inflammatory lesions. The Levaditi stain failed to reveal any treponemata.

The gall bladder was thickened, and adherent to surrounding structures.

The spleen weighed 525 gm. Its capsule was thickened, and there was a pronounced perisplenitis, with firm adhesions to the liver and adjacent parietes. Its consistency was firmer than normal, and it cut with increased resistance. The cut surface showed chronic passive congestion, increase of connective tissue, and Malphighian corpuscles which were less than normally prominent. Histologically, thickening of the capsule and trabeculæ, and rather marked atrophy of the parenchyma were observed—the latter

perhaps the result of the diffuse increase in supporting tissue. There were a few healed lesions containing calcium which were thought to represent old gummata.

The small intestine contained 355 cc. of clotted blood, and there was an area of capillary injection about 5 cm. in diameter situated in the posterior stomach wall near the cardia, but no varices were to be found in the lower esophagus or cardiac end of the stomach.

The kidneys were essentially normal.

The internal genitalia were not remarkable except that the uterus was unusually small. Histologically, the ovaries were normal and contained numbers of primordial ova.

The fractured humerus had healed completely by bony union (Figs. 3 and 4). Histologic examination of the bone showed irregularity of the cortex due to the presence of numerous bloodvessels leading from the periosteal to the medullary tissue; general thinning of the cortex and complete loss of its substance in areas of penetration by bloodvessels; thin, irregularly arranged trabeculæ; perivascular infiltration and intimal thickening of the smaller bloodvessels; and a low-grade proliferative inflammation of the periosteum which had resulted in osteogenesis in the cortical tissue.

Summary. Healed lesions of syphilis, probably congenital, in the bones, liver and spleen. In the liver the extensive scarring had given rise to biliary and portal obstruction, producing jaundice, ascites, and hemorrhage from the intestinal mucosa.

Review of the Literature. A thoroughly exhaustive research of the literature of tertiary visceral syphilis reproducing the clinical features of Banti's syndrome would involve a greater amount of labor than is warranted by the nature of the subject. The present review is reasonably thorough and comprehends perhaps the most important cases, but it must not be supposed to exhaust the available material. The bibliography cites, in addition to the principal papers, a few references which were found to have appreciable collateral value.

In view of the facts that Banti's syndrome often requires many years for its evolution, during which time it passes through various stages which are none too well defined, that it is prone to exhibit little understood variations from the general course which it is supposed to pursue, and that its right to a position as a definite pathological entity has never been firmly established, it has not been deemed wise to erect too rigid a set of criteria for classification of cases. Nevertheless, some difference of opinion is likely to arise among students of the subject with reference to the classification attempted here. It has been found expedient to divide the cases into three groups. The first group comprises those cases of syphilis simulating Banti's syndrome which have been acceptably reported and are regarded as satisfactory for both categories beyond reasonable doubt (Table I). The second group includes cases which are for the most part highly suggestive of syphilis simulating Banti's syndrome, but are nevertheless open to serious question from one or another standpoint (Table II). The third group embraces cases which are held to be definitely excluded from the category (Table

III). Many of the cases cited in the third group are included not because of their intrinsic merit, but because they have been called into question by previous writers on the subject.

Satisfactory Cases (*Table I*). Except as indicated in the table, these cases are well authenticated, and do not require extended comment.

TABLE I.—SATISFACTORY CASES.

Date.	Author.	No. of cases.	Comment.
1900	Osler[57,58]	2	One autopsy; see text.
1901	Cayley and Wynter[13]	1	Case report none too complete.
1902	Hocke[39]	1	Autopsy; the syphilis might be questioned.
1902	Chiari[15]	2	Cases 1 and 4 of his paper; see text.
1904	Hochhaus[38]	1	Autopsy.
1905	Caussade and Milhit[12]	1	Autopsy.
1911	Ridder[70]	1	
1911	Schmidt[73]	1	
1911	Weber[83]	1	Autopsy.
1912	Cattoretti[10]	1	Second stage, Banti syndrome; syphilis possibly questionable.
1912	Neuberg[56]	1	
1913	Urrutia[78]	1	
1914	Anderson[2]	1	
1914	Caussade and Levi-Frankel[11]	1	Autopsy.
1914	Hartwell[35]	1	Open to some question, especially the syphilis.
1914	Jeanselme and Schulmann[40]	1	
1914	Osler[59,60]	2	One autopsy; see text.
1914	Queyrat[65]	1	
1916	Giffen[31]	3	
1916	Vance[80]	1	Autopsy.
1917	Resio[67]	1	
1918	Eason[23]	1	
1918	Resio[68]	1	
1919	Fawcett[27]	1	Syphilis possibly questionable.
1919	Resio[69]	1	Autopsy.
1924	Gonzalez Olaechea[33]	1	
1925	Acuna and Maggi[1]	1	
1926	McCrae and Caven[47]	1	
1927	Bianchetti[7]	1	
1927	Maniel and Nee[45]	1	Syphilis somewhat questionable.
1929	Korns	1	Autopsy; case reported herewith.
		Total, 36	

To Osler[57,58] belongs the distinction of having recorded, in 1900, the first case of tertiary syphilis which reproduced the clinical features of Banti's syndrome. The autopsy report of the first case had been published in 1891 by Councilman.[93] In 1914, Osler[59,60] amplified his descriptions of these cases, and added two more.

Chiari[15] described 4 cases in all, but his Case III had already been recorded in detail by Hocke,[39] and the presentation of his second case is inadequate, particularly with reference to the anamnesis. His first and fourth cases are fairly satisfactory, although Leon-Kindberg[43] was inclined to look upon the evidence of syphilis as unconvincing. There were necropsies on all 4 cases.

Gonzalez Olaechea[33] states that in 1923 he reported another case similar to the one referred to here.

Questionable Cases (*Table II*). *A priori*, one would not expect to find cases prior to the time of Banti's contributions which could be recognized clearly today as Banti's syndrome. This is indeed the fact, but there are nevertheless many highly suggestive cases, some of which barely miss meeting the essential requirements.

TABLE II.—QUESTIONABLE CASES.

Date.	Author.	No. of cases.	Comment.
1876	Goldstein[32]	1	His Case 2; autopsy; see text.
1879	Deakin[22]	1	His Case 1; autopsy; see text.
1886	Strümpell[75]	1	Autopsy; see text.
1895	Carslaw[9]	1	Congenital syphilitic, aged eighteen years, with enlarged liver and spleen; no other details given.
1896	Coupland[19]	1	Autopsy; see text.
1902	Musser[54]	1	Case of cerebrospinal syphilis with intercurrent jaundice, hepatic and splenic enlargement, gastro-intestinal hemorrhages and moderate anemia.
1907	Thomas[77]	1	Possibly early stage of Banti's syndrome; see text.
1910	Hess[37]	3	His Cases 1, 5 and 6; inadequate case reports.
1910	Monaschkin[50]	1	Syphilis questionable; see text.
1910	Wagner[82]	1	Syphilis questionable.
1911	Fuhs[30]	1	Syphilis questionable.
1911	Vogel[81]	1	Not clearly Banti's syndrome.
1912	Lindt[46]	1	Both Banti and syphilis open to question.
1912	Perussia[64]	1	Discussion in text.
1912	Vallardi[79]	1	Discussion in text.
1914	French and Turner[29]	1	Case report inadequate.
1915	Krull[41]	2	His Case 2, syphilis, but not Banti's syndrome; his Case 3, evidence of syphilis only inferential; both cases autopsied.
1916	Clark[16]	1	Both syphilis and Banti's syndrome questionable.
1919	Courtois-Suffit and Giroux[20]	4	Case reports incomplete.
1919	Symmers, Gettler and Johnson[76]	1	Their Case 4; see text.
1920	Miller[49]	1	Probably not syphilitic.
1924	Rohacek[71]	1	Not clearly Banti's syndrome.
1925	Farley[26]	1	Not clearly Banti's syndrome.
1927	Curschmann[21]	1	Description inadequate.
		Total, 30	

Goldstein's[32] Case 2 had syphilis undoubtedly, and manifested some of the clinical features of Banti's syndrome, namely, icterus, enlargement of the liver and spleen, and late ascites. Necropsy showed that the liver was not much enlarged, and contained gummata; and that the spleen and lymph nodes were enlarged. His description, however, is so wanting in detail that one can do no more than classify the case as suggestive.

Deakin's[22] Case 1 is even more suggestive than Goldstein's, but

his description is also inadequate, particularly with respect to the history. The patient had anemia, ascites, slight icterus, and enlargement of the liver and spleen. Death was caused by hematemesis. Necropsy showed that the left lobe of the liver was nearly equal in size to the right, and that the organ contained many gummata, one of which was obstructing the portal vein. Glisson's capsule was thickened and firmly adherent to the stomach and diaphragm, and there was a proportionate degree of perisplenitis. The spleen weighed 680 gm. No varices were found in the gastrointestinal tract.

Strümpell's[75] case, as Peiser[63] reports it, is also inadequately described. The patient, who was aged fifty years, was said to have had splenomegaly twenty-two years earlier. He had been ill for two years with fever and pain. He had an enlarged liver and spleen, and while under observation developed ascites and slight icterus. Necropsy revealed syphilis of the liver, chronic perihepatitis and perisplenitis, and splenomegaly.

Coupland's[19] case is of especial interest because it has been referred to by so many writers, but his description, which is extremely brief, by no means fulfills even the most elementary requirements of Banti's syndrome. It was simply a patient with enlarged spleen and anemia who improved greatly after splenectomy, but died two years later from hematemesis. The necropsy disclosed a typically scarred liver and varices of the rectum and esophagus.

Thomas's[77] patient gave a history of a chancre, and of weakness and epistaxis. He was pale, and his liver was greatly enlarged, filling the entire right upper quadrant of the abdomen; the spleen extended 16 cm. below the costal margin. Antisyphilitic treatment effected great reduction of the hepatic enlargement, slight reduction of the splenic enlargement, and pronounced improvement of the patient's general condition. Except for the excessive amount of hepatic enlargement, this case may be thought to reproduce an early stage of Banti's syndrome fairly acceptably, but the case report is deficient in respect to several essential details.

Monaschkin's[50] case presented many of the clinical features of Banti's syndrome, but, as he himself indicates, the evidence of syphilis is incomplete. However, two of his reasons for excluding syphilis, namely, that antisyphilitic treatment was ineffectual, and that the blood changes were not characteristic, especially because there was leukopenia rather than leukocytosis, are invalid, as the accumulated experience with cases of this kind has demonstrated conclusively. The Wassermann reaction was positive, but as an isolated observation this cannot be regarded as proof of syphilis.

The cases reported by Perussia[64] and Vallardi[79] are as baffling as they are interesting. Both were diagnosed "anemia splenica," but in neither was there anything in the history, physical examination, or serological tests, to suggest syphilis. Notwithstanding this fact, both patients were vastly improved by intravenous injections of

salvarsan. Vallardi's patient had had malaria two years before, but no plasmodia were demonstrable while he was under observation. Vallardi regarded syphilis as definitely excluded in his own case; Perussia contented himself with speculation. Both cases defy exact classification.

Symmers, Gettler and Johnson[76] present 6 cases, but only one of them (their Case 4) is described in sufficient detail to warrant consideration. Certain features of this case incline one to include it among the number of cases regarded as proved, but unfortunately the published report is wanting in several important respects.

Cases Not Included (*Table III*). Of the cases cited by Barthelemy,[5] only that of Gouraud is worthy of notice, but the question of what part the known malaria played in the etiology cannot be answered. The patient was a girl, aged thirteen years, who had suffered gradual enlargement of the abdomen; the spleen was enormous, the liver small. Icterus appeared during the last month of life. Death occurred from rupture of a circum-umbilical varix. At autopsy, the liver was found to be small (880 gm.), and was umbilicated and cut through by thick fibrous bands. The spleen measured 22 by 12 cm. and had a thickened capsule.

TABLE III.—CASES NOT INCLUDED.

Date.	Author.	No. of cases.	Comment.	
1870	Moxon[52]	1	Autopsy; not Banti's syndrome.	
1876	Goldstein[32]	1	His Case 1; autopsy; no splenomegaly.	
1877	Bramwell[8]	1	Inadequately described.	
1883	Engel[25]	1	Syphilitic hepatitis, not Banti's syndrome.	
1884	(Barthelemy)[5]			
	Barth	1	Not Banti's syndrome.	
	Berne	1	Not Banti's syndrome.	
	Crequy	1	Not Banti's syndrome.	
	Dittrich	2	Both autopsied; not Banti's syndrome.	
	Dowse	3	Not Banti's syndrome.	
	Gouraud (1863)	1	Autopsy; see text.	
	Tissier	1	Not Banti's syndrome.	
1886	Bartels[4]	1	Case report inadequate.	
1886	Fournier[28]	1	Case report inadequate.	
1886	(Peiser)[61]			
	Frerichs (1861)	4	Three autopsies	Discussion in text.
	Hjelt (1861)	1	Autopsy	
	Chvostek (1863)	1		
	Vecchi (1869)	1		
	Goodbridge (1871)	1	Autopsy.	
	Riegel (1872)	1	Autopsy	
	Picot (1872)	1	Autopsy	
	Key (1873)	1	Autopsy	
	Loewenfeld (1873)	2	Both autopsied	
	Lacombe (1873)	1	Autopsy	
	Martineau (1875)	1	Autopsy	
	Dusaussay (1876)	1		
	Key (1878)	1	Autopsy	
	Chvostek (1881)	11	Eight autopsies	
	Kahl	2	Both autopsied	
	Schützenberger	1		

Date.	Author.	No. of cases.	Comment.
1891	Chauffard[14]	1	A congenitally syphilitic baby with enlarged liver and spleen; not Banti's syndrome.
1894	Otto[61]	7	Secondary syphilis with icterus; see text.
1897	Cole[17]	2	Spleen not mentioned.
1897	Schlichthorst[72]	1	Marchand's[46] Case 1; autopsy; syphilis not proved.
1900	Guerin[34]	1	Not Banti's syndrome.
1900	Menetrier[48]	1	Autopsy; hypertrophic cirrhosis; see text.
1900	Peabody[62]	1	Not Banti's syndrome.
1901	Einhorn[24]	10	Not Banti's syndrome.
1902	Stockton[74]	3	No splenomegaly.
1902	Weinberger[85]	1	No evidence of syphilis.
1903	Marchand[46]	2	One autopsy; see text.
1904	Bernard[6]	1	Simulated hypertrophic biliary cirrhosis.
1905	Aspelin[3]	4	Banti's syndrome, but not syphilis.
1908	Naegeli[55]	1	Case not adequately reported.
1910	Hayn and Schmitt[36]	1	Laboratory statistics; no clinical report.
1910	Hess[37]	3	His Cases 2, 3 and 4; syphilis questionable and case reports inadequate.
1911	Moore[51]	1	Autopsy; no evidence of syphilis.
1912	Mullally[52]	1	Autopsy; not Banti's syndrome.
1913	Core[18]	1	Case report inadequate.
1914	Lemaire[42]	1	Acquired hemolytic icterus; not Banti's syndrome.
1914	Leon-Kindberg[43]	1	No evidence of syphilis.
1919	Symmers, Gettler and Johnson[76]	5	Their Cases 1, 2, 3, 5 and 6, all inadequately described.
1919	Weil[84]	5	His Cases 6, 7, 8, 11 and 12; descriptions meager; syphilis not proved.
1926	Raynaud, Nanta and Lacroix[66]	2	Banti's syndrome, but not syphilis.
	Total,	104	

With the exception of Strümpell's and Deakin's cases, both of which have been discussed under Table II, it is impossible to construe as Banti's syndrome any of the numerous cases catalogued by Peiser.[63] It is perhaps correct to say that all were cases of syphilis of the liver, but it would be unprofitable to attempt further classification.

Syphilitic icterus is Otto's[61] thesis. He refers at some length to the cases of Vecchi, von Jastrowitz, Picot, von Schleuthauer, Beck, and Roth and Tommasi, which obviously do not fall within the category of Banti's syndrome, and reports 7 cases of secondary syphilis, all with icterus, none of which simulated Banti's syndrome.

The case recorded by Menetrier[48] might have been mistaken for Banti's syndrome had it not been for the enormously enlarged liver (2800 gm.), which was the seat of a hypertrophic cirrhosis, and was studded with gummata. The spleen weighed 1750 gm. The patient was a woman, aged forty-six years, a chronic alcoholic. Her illness

of three years' duration was characterized by painless swelling of the abdomen, epistaxis, and secondary anemia; toward the end ascites developed, but never icterus.

Marchand's paper[46] demands particular attention because of the fact that it has been referred to by so many writers on the subject of syphilis and Banti's syndrome. In his first case, which was really Schlichthorst's, there was no satisfactory proof of syphilis. His second case was that of a boy whose illness extended from his thirteenth to his sixteenth years, when he died of secondary anemia from repeated hematemesis. He had chronic splenomegaly, ascites, leukopenia, secondary anemia, and slight enlargement of the liver, but no icterus. At necropsy the spleen weighed 830 gm. and the liver 1390 gm. The latter showed cirrhosis and granular atrophy. No mention of gummata was made. That this was clinically a fairly good case of Banti's syndrome cannot be questioned seriously, but Marchand's contention that congenital syphilis played an etiologic rôle was based purely upon rather precarious anatomic grounds, and is unconvincing. His third case is invalidated by a history of malaria and the presence of widespread tuberculosis of the lungs and intestines, as well as by the fact that the evidence of syphilis was merely hypothetical. It was presumably to this case that Schmidt[73] referred when he said that one of Marchand's cases proved later to be kala-azar, for Marchand's first and second cases were controlled by autopsy. There is no justification, therefore, for including any of Marchand's cases in the category of Banti's syndrome reproduced by syphilis.

Discussion. One carries away from a study of the literature of this subject a number of rather definite impressions. Rolleston's[119] observations with reference to the character of the pathologic alterations in the liver can be appreciated at their true value. Of the polymorphic lesions which he describes the sclerogummatous form occurs most frequently. The liver is reduced in size (weights as low as 700 gm. have been recorded) and is so "widely fissured and lobulated" by linear and stellate cicatrices, the residua of healed gummata, "that the shape of the liver may be altered out of all recognition." In this state it has been aptly termed *foie ficelé* by the French writers. "The relative size of the two chief lobes of the liver may be greatly altered; thus, the left lobe may be almost entirely destroyed by fibrous contraction, or enlarged from gummatous infiltration or from hyperplasia of the liver substance to compensate for extreme destruction of the right lobe." Rolleston attributes the splenomegaly to amyloidosis or gummatous infiltration, but in the necropsy protocols of cases simulating Banti's syndrome which I have examined, it appears that a relatively simple interstitial fibrosis is the usual cause. Rolleston refers to Cheadle's statement that syphilis is the most important cause of perihepatitis, but his own experience is that "gummas commonly

cause local perihepatitis, but that syphilitic infection is quite an exceptional cause of universal perihepatitis." In the group of cases here reviewed the evidence favors Cheadle's opinion. Thickening not only of Glisson's capsule, but also of the capsule of the spleen, with dense and extensive synechiæ to the diaphragm and adjacent viscera is of almost universal occurrence. In Vance's[80] case the left half of the diaphragm was said to be 3½ inches thick! In my own case the liver was completely hidden in a nest of dense scar tissue, of which the diaphragm formed an integral part. Surgeons undertaking splenectomy almost invariably experience great difficulty in freeing the spleen from its numerous adventitious attachments. Further discussion relating to pathology may be found in the papers of Chauffard,[14] Grenier,[100] and Moschcowitz.[110]

The secondary anemia, leukopenia, and relative lymphocytosis characteristic of Banti's syndrome are found likewise in tertiary hepatic syphilis which reproduces that syndrome. Intermittent jaundice, usually mild, and generally obstructive in type; recurrent ascites; hemorrhage, either from the nose or stomach; and pain in the upper quarters of the abdomen, are of frequent occurrence. Schrager[120] and Rolleston,[119] among others, have emphasized the importance of pain as a symptom of syphilitic hepatitis. The general semeiology has been discussed at length by Gerhardt,[98] Peiser,[63] Otto,[61] Weber,[83] Vance,[80] and others.

The diagnostic criteria of Banti's syndrome need not be recited, nor should it be necessary to insist upon the institution of antisyphilitic treatment in cases of Banti's syndrome in which syphilis is known or can be proved, but it is necessary to insist with all possible emphasis upon a thorough trial of antisyphilitic treatment in every case of Banti's syndrome before syphilis is finally excluded. No other single fact emerges so imperatively from the literature of this subject. Time and time again the fundamental rôle of syphilis has been overlooked because it was not suggested by the history, by unequivocal physical signs, or by serologic tests, and was only discovered at operation or autopsy. The well-known fact that in the late stages of the syndrome, when most of the liver has been replaced by scar tissue, antisyphilitic treatment may be largely or wholly ineffectual, in no wise constitutes an exception to the rule demanding a therapeutic test.

In the treatment, potassium iodid, bismuth and mercury should be given first consideration. The most conspicuous therapeutic successes with mercury and potassium iodid, separately or in combination, are those which have been reported by Guerin,[34] Chauffard,[14] Thomas,[77] Anderson,[2] Clark,[16] and McCrae and Caven.[47] Syphilologists of today would perhaps frown upon the use of arsenicals, yet a great many of these cases have been treated energetically and successfully with one or another of the arsphenamins, for example, Perussia,[64] Vallardi,[79] Schmidt,[73] Curschmann,[21] Urrutia,[78]

Cattoretti,[10] Jeanselme and Schulmann.[40] Two years after Schmidt's report, Curschmann[94] stated that the patient continued to enjoy excellent health. In the earlier stages of the disease, when great benefit is to be expected from antisyphilitic treatment, splenectomy is rarely indicated, but this is not necessarily true in the later stages, even if the medicinal treatment continues to be to a certain extent efficacious. Coupland's[19] experience first called attention to the fact, subsequently emphasized by Giffen[31] and others, that under certain circumstances splenectomy is an essential part of the treatment.

Summary. A case of tertiary syphilis of the liver which manifested itself as Banti's syndrome in the terminal stages is reported.

The literature of tertiary syphilis of the liver reproducing the clinical features of Banti's syndrome is reviewed, from which 36 approved cases, and 30 questionable cases, are collected. One hundred four additional cases, many of which have been cited frequently in the literature, are excluded from the category.

The pathology, semeiology and treatment are discussed briefly. In particular, the great importance of applying the therapeutic test to every case of Banti's syndrome before excluding syphilis as a possible etiologic factor is reëmphasized.

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AN EXPERIMENTAL STUDY OF THE REACTION OF THE CONTENTS OF THE TERMINAL PORTION OF THE ILEUM.*

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Among the factors which influence the reaction of the contents of the gastrointestinal tract may be mentioned saliva, food, gastric secretion, bile, pancreatic juice, intestinal secretions, bacterial putrefaction and the cleavage products of digestion. Statements to the effect that one type of food increases acidity and another decreases acidity are common, but there are few experimental data to show that the reaction of the contents of the intestinal tract can be appreciably changed by variations in the normal diet. It was thought that a study of the hydrogen-ion concentration of the intestinal contents, at frequent intervals throughout the process of digestion of various kinds of food, might throw some light on the subject.

A number of the questions which suggest themselves are: (1) What is the hydrogen-ion concentration of the contents of the terminal portion of the ileum of a dog fed a well-balanced diet at various periods during the process of digestion? (2) What changes in the hydrogen-ion concentration occur when the protein-fat-carbohydrate ratios are varied? (3) What, if any, relationship is there between the hydrogen-ion concentration and the time after the intake of food?

Literature. McClendon, Bissel, Lowe and Meyer (1920) after a thorough review of the literature on this subject concluded that there is lack of agreement in regard to the reaction of the intestinal contents and the changes brought about by various diets. Since then, however, other significant facts have been reported.

Okada and Arai (1922) found the reaction of the contents of the ileum of dogs to vary between hydrogen-ion concentration 6.59 and 7.83; readings were taken one, two and three hours after the dogs had been fed a pound of meat.

Abrahamson and Miller (1925) fed adult male albino rats different diets, some consisting largely of carbohydrates, some mainly of protein and others mainly of fat. They observed an average variation in the hydrogen-ion concentration of only 0.1 to 0.2 in the stomach and small intestine. Their readings uniformly showed acid in the lower half of the small intestine. The animals were killed several hours after their last meal and the hydrogen-ion concentration of the contents was determined colorimetrically.

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Redman, Willimott and Wokes (1927) found the average hydrogen-ion concentration of the contents of the ileum of guinea pigs to be pH 7.4, while that of normal adult rats was 6.8 and of young rats (one to three months old) 7. High-fat and low-fat types of rachitogenic diets when fed to rats induced greater acidity throughout the intestinal tract if vitamin D was added, but in the absence of vitamin D the fecal reaction became alkaline. They could not produce marked alteration in the intestinal hydrogen-ion concentration by varying the protein-fat-carbohydrate ratios of normal diets. It was found that the acidity of the contents of the stomach and duodenum tends to increase during the first four hours after the ingestion of a meal. In the remainder of the tract, however, an appreciable difference could not be observed in the hydrogen-ion concentration obtained when the time between feeding and death was between one and a half and four and a half hours. Only when food was withheld for as long as seventeen hours was the acidity much greater throughout the small intestine. A hydrogen electrode was used for making the determinations. Yoder (1927), working with the quinhydrone electrode, obtained similar results. He did not present readings for animals on normal diets.

Grayzel and Miller (1928) summarized their work on dogs as follows: "The reaction of the intestinal contents of dogs fed on a normal mixed diet is acid practically throughout the entire length of the tract, the cecum and colon showing somewhat less constancy in the results than the other levels of the tract. The hydrogen-ion concentration of the small intestine varies between 5.7 and 6.6. The reaction of the intestinal contents of dogs fed high-fat, protein, or carbohydrate diets is practically within the normal range of each level of the tract." The dogs were killed by intravenous injections of amytal four to six hours after their last meal. The abdominal cavity was then opened and the small intestine divided into sections, 60 cm. in length. The reaction of the contents of each section was then determined. It was shown that dilution did not appreciably affect the hydrogen-ion concentration and that the readings by the colorimetric and electrometric methods agreed closely. The colorimetric readings were on the average about pH 0.2 lower than those obtained by the electrometric methods.

While working on intestinal absorption, Hosoi, Alvarez and Mann (1928) observed that the intestinal contents of dogs were neutral except on one occasion when hashed meat was fed; the contents then had a slightly alkaline reaction. They used dogs in which the colon had been removed and the ileum anastomosed to the rectum. The reaction of the contents thus obtained was determined with litmus paper. Childrey, during the study of a similar problem, found the contents of the small intestine of dogs to be alkaline to litmus in the majority of instances.

Method of Procedure. Three apparently healthy dogs were chosen for study. They were prepared by an operation devised by Bollman and Mann so that the contents of the ileum could be readily obtained at frequent intervals. Two of the dogs had fistulas formed by resecting a section of ileum about 5 cm. long and about 15 cm. from the ileocecal juncture. The blood supply to the resected portion was maintained, the continuity of the tract completed by means of an end-to-end anastomosis, and the fistula formed by means of an end-to-side anastomosis between the resected portion and the ileum immediately below the site of the end-to-end anastomosis. The important step in the operation is to turn the resected section of bowel so that the peristaltic impulses pass, from without, in toward the ileum. Thus little, if any, intestinal content passes out onto the skin and the wound will usually heal by first intention and the dogs can be kept in good condition.

The third dog was prepared by a method which required a two-stage operation: removal of the colon and an end-to-end anastomosis between the terminal portion of the ileum and the rectum and removing the rectum and joining the ileum to the anus. The end result of this operation was just as satisfactory as that of the other operation but it required more time and was technically more difficult. Before selecting the operations described several other operations were tried and found to be impractical or unsatisfactory.

Determinations of hydrogen-ion concentration were not made until at least two weeks after operation at which time the dogs were apparently normal.

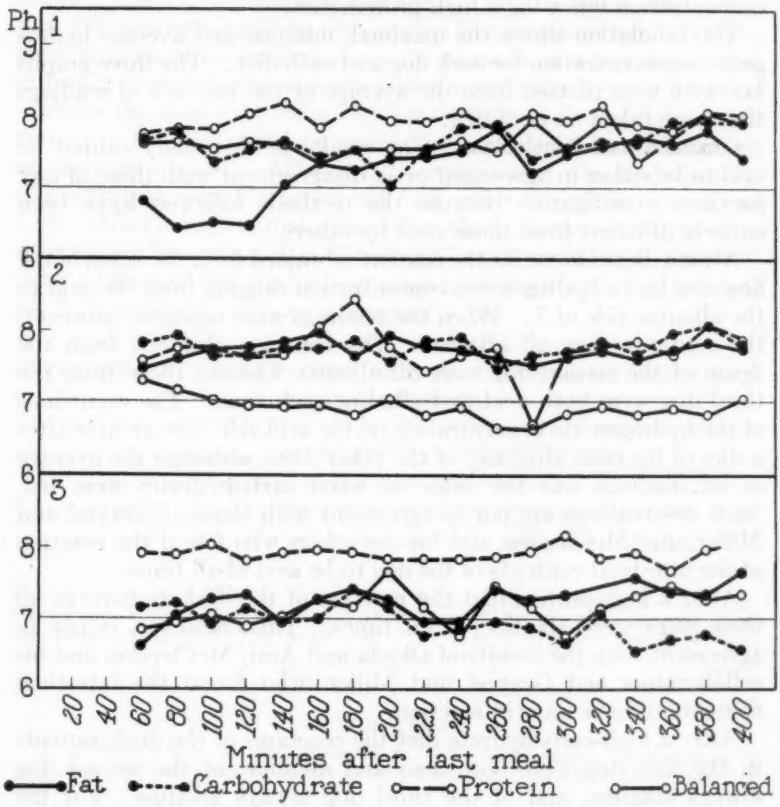
The diets chosen were: (1) High-fat in the form of fat horse meat; (2) high-protein in the form of lean horse meat; (3) high-carbohydrate in the form of cracker crumbs, skimmed milk and Karo syrup in proper proportions to make a thin paste; (4) whole milk. In each instance the dog was fed a given diet for two days and determinations of hydrogen-ion concentration were made on the third day. On the days that examinations were to be made the dogs were fed as much as they would eat in twenty minutes.

Determinations of hydrogen-ion concentration were made every twenty minutes beginning one hour after the last meal and continuing as long as sufficient material could be obtained, usually about seven hours. The contents were obtained by inserting a small rubber tube into the ileum and either aspirating or allowing the material to flow out, depending on its consistence. Whenever necessary a little distilled water was injected to aid in the collection of the material.

The hydrogen-ion concentration was determined with the aid of the quinhydrone electrode introduced by Biilmann (1921) and by a Leeds and Northrup potentiometer. Robinson(1925) compared the results obtained with the hydrogen and quinhydrone electrodes on a series of specimens of feces whose hydrogen-ion concentration

ranged from pH 5 to 7.8 and found the difference to be 0 to 0.3 with an average of less than 0.1.

After one set of observations had been completed the process was repeated and an average of the two used to chart a curve of the hydrogen-ion concentration at different intervals after a meal. More than 400 determinations were made.



The hydrogen-ion concentration of contents of the ileum of three dogs.

Results. After a high-fat meal the contents obtained from the ileum were yellow and of a semifluid consistence. The hydrogen-ion concentration varied between pH 5.7 and 8.15 with an average of 7.42.

After a high-protein meal a dark-brown homogeneous fluid was obtained. The hydrogen-ion concentration varied between pH 7.18 and 8.49 with an average of 7.86. These results were the most constant obtained.

The hydrogen-ion concentration of the ileal content, following a high-carbohydrate diet, was less constant than after a high-protein meal. It varied between pH 6.22 and 8.37 with an average of 7.42,

which was the same as the average following a high-fat diet. The material obtained was semifluid, containing yellow flakes.

After a diet of whole milk the ileal contents were fluid with bright yellow flakes similar to that noticed after a carbohydrate meal. The hydrogen-ion concentration varied between pH 6.33 and 8.08, with an average of 7.86, which was the same as the average hydrogen-ion concentration following a high-protein diet.

The tabulation shows the maximal, minimal and average hydrogen-ion concentration for each dog and each diet. The three graphs herewith were plotted from the average of the two sets of readings that were taken on each dog.

Comment and Conclusions. The results of this study cannot be said to be either in agreement or in disagreement with those of any previous investigators because the methods followed have been entirely different from those used by others.

After a diet of horse fat the contents obtained from the ileum of the first dog had a hydrogen-ion concentration ranging from the acid to the alkaline side of 7. When the readings were repeated, however, the contents were all alkaline. The contents obtained from the ileum of the second dog were all alkaline whereas those from the third dog were both acid and alkaline each time. The excursions of the hydrogen-ion concentration on the acid side were greater after a diet of fat than after any of the other diets, although the average of all readings was the same as when carbohydrates were fed. Such observations are not in agreement with those of Grayzel and Miller, and McClendon and his coworkers who found the reaction of the intestinal contents of the dog to be acid at all times.

After a high-protein diet the reaction of the ileal contents of all three dogs were alkaline at all times. This, however, is not in agreement with the results of Okada and Arai, McClendon and his collaborators and Grayzel and Miller, who found the intestinal contents to have an acid reaction.

After a high-carbohydrate diet the reactions of the ileal contents in the first dog were both acid and alkaline, of the second dog always alkaline, and of the third dog always alkaline. For the second dog all the readings showed acid the first day but when the study was repeated, both acid and alkaline results were obtained. Acid and alkaline results were also obtained when the third dog was studied.

Several possible sources of variation in readings should be mentioned: (1) The exposed intestinal tract is open to infection; (2) irritation caused by inserting a tube into the ileum frequently may give rise to variations in the amount of intestinal secretion; (3) in the early and late periods of observation only a scant amount of content is obtainable. There is no evidence, however, that these possible variations vitiated the results appreciably.

These data are presented without explanation, for to explain them would require a comprehensive study of the chemistry and probably

the bacteriology of the gastrointestinal tract and also a detailed study of the reactions of other portions of the tract from the stomach to the rectum.

Summary. Observations were limited to the contents of the terminal portion of the ileum of the dog. The dogs were prepared so that the contents could be obtained at frequent intervals. Thus a large number of determinations could be made on a few dogs. The influence of anesthesia or death was eliminated.

When the dogs were fed a high-fat diet the hydrogen-ion concentration of the ileal contents varied between pH 5.71 and 8.15 with an average of 7.42. After a high-protein diet the hydrogen-ion concentration varied between pH 7.18 and 8.49 with an average of 7.86. After a high-carbohydrate diet the hydrogen-ion concentration varied between pH 6.22 and 8.37 with an average pH 7.42. After a balanced diet the hydrogen-ion concentration varied between pH 6.33 and 8.08, with an average of 7.86.

HYDROGEN-ION CONCENTRATION OF ILEAL CONTENTS OF THREE DOGS ON VARIOUS DIETS.

	High-fat diet.			High-protein diet.			High-carbohydrate diet.			Balanced diet.		
	Maximal, pH.	Minimal, pH.	Average, pH.	Maximal, pH.	Minimal, pH.	Average, pH.	Maximal, pH.	Minimal, pH.	Average, pH.	Maximal, pH.	Minimal, pH.	Average, pH.
First dog	8.01	5.71	7.27	8.49	7.37	7.95	7.15	6.89	7.63	8.08	7.25	7.67
Second dog	8.15	7.35	7.71	8.45	7.18	7.73	8.37	7.22	7.76	8.00	6.33	6.96
Third dog	7.67	5.81	7.30	8.18	7.67	7.90	7.43	6.22	6.87	7.83	6.59	7.27
Average	..	..	7.42	..	..	7.86	..	..	7.42	..	..	7.86

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FATAL EMETIN POISONING, DUE TO CUMULATIVE ACTION, IN AMŒBIC DYSENTERY.

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In view of the increasing prevalence of amœbiasis throughout the United States, as has been pointed out by Kofoid,[1] Dowling,[2] Smithies,[3] and others, it is desirable to realize the importance of this disease, no longer tropical, and the occasional accidents in its treatment. The Gulf and Pacific Coast States, still lead with the greatest number of infections, but it is surprising to note the great number of carriers found in Philadelphia by de Rivas and Fife[4] and in Chicago by Smithies.[3]

It is a regrettable fact that so little is known about the chemistry and pharmacology of emetin, and its action on the Entamœba histolytica. It is not the purpose of this paper to add new experimental data to our knowledge of this drug, but to point out the discrepancies and conflictions of opinion that occur in the literature regarding the action, dosage and toxicity of emetin. I also wish to show that poisoning, which may be fatal, may and does occur even in doses much smaller than the heretofore considered minimal lethal dose.

Summary of Case Record. The patient was a female, aged twenty-one years, a university student. In the latter part of August, 1928, she spent a few days in the mountains and drank water from a glacial stream. On returning to Seattle early in September, she began to have our or five watery stools a day, accompanied by cramp-like pains in the epigastrium, and by a respiratory embarrassment which would cause her to sit up to breathe. She began to lose weight slowly, but this was attributed to her loss of appetite and decreased food intake. The physical examination was completely negative, except for a slight tenderness over the course of the colon. The body weight was about 100 pounds.

She entered the hospital on January 2, 1929, for diagnosis and treatment. The laboratory reported a hemoglobin of 82 per cent; white blood count, 8600 cells per c.mm.; a differential count of 70 polymorphonuclear leukocytes and 30 lymphocytes. The Wassermann reaction was negative. The urine showed a faint trace of albumin. Entamœba histolytica was found in the stool.

The following treatment was instituted: The large bowel was irrigated twice daily with a 1 to 3000 solution of quinin bisulphate, and emetin hydrochlorid, 0.02 gm., given intravenously morning and night for ten days (20 injections). After this time no amœba were found in the stool. There was no nausea, vomiting or other gastrointestinal symptoms at any time. The bowels moved two or three times daily without pain, the stools being soft, but well formed. The tenderness in the abdomen had disappeared. After a rest period of one week, during which time one quinin irrigation was given daily, the emetin was resumed and given for four days only (8 injec-

tions). On January 23 the patient left the hospital with amœba-free stools after repeated examinations since January 15.

Shortly after returning home amœbæ were again found and the diarrhea and tenderness returned. She also noted that she tired easily, and had some vague pain in the legs when walking to and from her classes about the campus. On February 2 she was readmitted to the hospital. The following treatment was ordered, modified after that of Bethea.[5]

First Period. Five days: 0.065 gm. of emetin hydrochlorid injected daily into the deltoid muscles. No other medication during this period. Full typhoid diet up to 3000 calories daily.

Second Period. Ten days: Emetin continued as above; 2.3 gm. of ipecac given daily in enteric coated pills. These pills were freshly prepared. During this second period the patient was given a daily colonic irrigation of 2 gm. of quinin sulphate in ½ gallon of warm water. The typhoid diet was continued, but while the ipecac pills were being given at bedtime, the patient received soft diet during the day up to 1 P.M., after which time she received nothing but simple liquids, as water, tea, black coffee, bouillon or ginger ale.

The treatment for the first period was carried out, and the first three days of the second period, when treatment was discontinued due to vomiting.

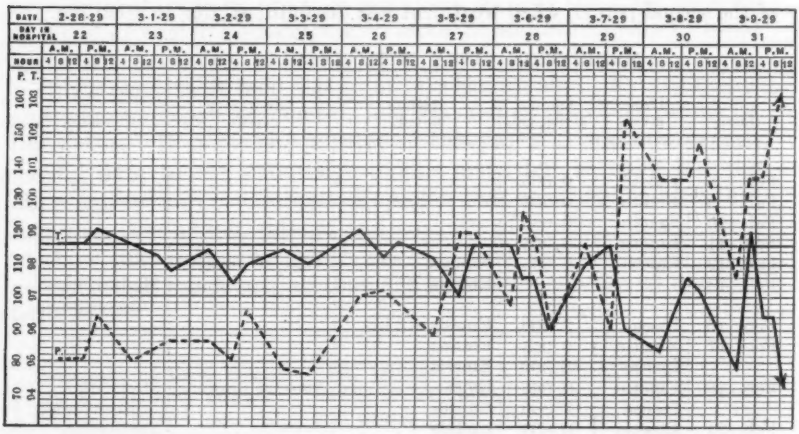
MEDICATION GIVEN WITH RESULTS NOTED.

Date.	Drugs given.	Amount given, gm.	Results noted.	Laboratory report.	Remarks.
Feb. 8	Emetin	0.065			
Feb. 9	Emetin	0.065			
Feb. 10	Emetin	0.065			
Feb. 11	Emetin	0.065			
Feb. 12	Emetin	0.065	Nausea	Amœbæ present	
Feb. 13	...	...	Emesis	.....	Medication discontinued
Feb. 16	Ipecac	2.300	Emesis in 3 hrs.		
Feb. 17	Emetin	0.065	Emesis		
	Ipecac	2.300	Emesis		
Feb. 18	Emetin	0.065	Emesis	Amœbæ present	Medication discontinued.
	Ipecac	2.300	Emesis		
Feb. 21	Emetin	0.065	Emesis	.....	Medication discontinued.
	Ipecac	2.300	Emesis		
Feb. 25	Emetin	0.020*	Nausea	Amœbæ present; few pus cells; blood 1+	
Feb. 26	Emetin	0.020*	Appetite poor; no nausea	.....	Medication discontinued.
Feb. 28	Emetin	0.020*	Appetite poor; restless	.....	Medication discontinued.
Mar. 2	Emetin	0.020*	Appetite poor; restless		
Mar. 3	Emetin	0.020*	Appetite poor; restless	Amœbæ present; few pus cells	Medication discontinued sedatives ordered.
Mar. 7	...	...	.....	Amœbæ present; blood 2+	

* Twice daily.

The chronologic data in table shows the amount of medication given daily and the results noted.

On March 3, after spending several restless nights, the patient asked for a rest period, as she was feeling weaker. The pulse was good, averaged 80 to 85; the temperature and respiratory rate were normal. Sedatives were given in small amounts, with poor results. On March 4 the pulse rose to 100; on March 5, to 120 and the temperature fell to 97° F. She was weaker, more restless and developed symptoms of a mild peripheral neuritis. From this date the temperature continued to fall, associated with a corresponding increase in the pulse and respiratory rate. (See graphic chart.) On March 7 a consultation was held. There was evidence of a mild myocarditis and digalen was given every four hours. The prognosis was very good. On the morning of March 9 the respirations became rapid, the pulse very weak, and the patient became cyanotic; 500 cc. of 5 per cent glucose in physiologically normal saline were given intravenously, with 12 units of insulin. She promptly felt relieved and the symptoms disappeared. The consultant again pronounced the heart to be in good condition and made a very favorable prognosis. That evening the symptoms returned, but were less severe. An intravenous injection of saline and glucose was started and after 200 cc. were given she showed no improvement. Gradually the respira-



tions became very embarrassed, cyanosis deepened and the pulse could not be felt. At this turn in her condition adrenalin, in 1 to 10,000 solution, and caffein sodium benzoate were given slowly intravenously (1 cc. in two minutes), being injected with the glucose, without response. She expired in a few minutes.

Autopsy. At autopsy little was found except at the point of entrance of the ileum into the cecum, where there were several scars, as from healed ulcers. Just lateral to the opening of the ileum there was a small ulcer 0.66 cm. in diameter. The entire large intestine was examined for ulcers. No other ulcers were found. There were several scars as from healed ulcers. The arterial supply to the intestinal tract was normal. The veins were dilated throughout to about one and a half to two times normal size. The heart grossly showed a slight myocarditis. The microscopic examination of the tissues showed a marked parenchymatous degeneration of the liver, most marked about the central veins. There was an acute diffuse nephritis and an acute parenchymatous degeneration of the adrenals. The spleen showed an acute hyperplasia due to toxemia. Death was apparently due to a condition of shock, probably produced by the cumulative action of some toxic substance.

Summary of Case. A young female, weighing about 100 pounds (37 kg.) received 0.56 gm. of emetin hydrochlorid from January 2 to January 23: During the second admission to the hospital she received 0.72 gm. of emetin, from February 2 to March 3. The total amount of the drug received, over a period of about two months, was 1.28 gm., or 0.034 gm. per kg. of body weight. After the first series of treatments the disease appeared to be cured. There was a relapse, and she returned to the hospital for further treatment. This was carried out with but moderate success, when the emetin was discontinued, due to general debility of the patient. Six days after the drug was discontinued, death occurred from a vasomotor collapse and heart failure, brought on by the cumulative action of emetin. The autopsy findings showed only slight anatomic changes.

Discussion. In 1916 Levy and Rowntree[6] reported the first case of fatal emetin poisoning. This prompted them to investigate the toxicity of various commercial preparations of emetin, by experiments on animals. They found that a daily dose of 5 mg. (3 to 4 mg. per kg.) to be fatal in rabbits in five to six days. Necropsy revealed but slight anatomic changes. The effect of intravenous injections depended on the quantity injected, its dilution, the rate of injection and to a lesser extent on the preparation employed.

This brings up the question as to what the minimal lethal dose of emetin may be. Vedder[7] reported it to be 2.5 mg. per kg. in rabbits, when given intravenously. Walters and Koch,[8] in their experiments found it to be 5 mg. per kg., and they also demonstrated the cumulative action of the drug. They showed that if one-half the minimal lethal dose were repeated daily subcutaneously, it would be fatal after an amount equivalent to two and one-half times the minimal lethal dose had been given. On this basis, they estimated the minimal lethal dose for man to be 0.06 gm. daily for twenty-one days (1.37 gm.). Guglielmetti,[9] perhaps, has estimated the dose of the drug more accurately than other investigators. He found it not advisable to go over 0.15 gm. per day for five or six consecutive days, or 0.10 gm. for eight to ten days, or 0.05 gm. for fifteen to twenty days. The intervals between the series should be long. Fatal toxic action is liable with 0.6 gm. at one time, and death is practically certain with 1.2 gm. at one time.

The disparity in the minimal lethal dose in laboratory animals may be noted in the above quotations. Matsuoka[10] has demonstrated with rats, rabbits and dogs, that individual differences exist in determining the minimal lethal dose, and hence, the conclusion of the minimal lethal dose cannot be applied to the human system, after it has been found by animal experimentation. This point has also been stressed by other investigators.

The minimal lethal doses thus far defined as applying to man are not sufficient, as our patient had considerably less emetin, over a

longer period of time, with frequent interruptions in the treatment, and yet had passed the minimal lethal dose a week before death had occurred, the drug not being given during the last week of life. That much larger doses are given I need but quote Smithies[3] who, as late as 1928, advised giving emetin 0.02 gm. three times daily, for two days, and after that increasing by 0.02 gm. after each dose until 0.2 gm. are given three times daily. From my own experience this is much too large a dose and far exceeds the minimal lethal doses established by Guglielmetti, Walters and Kock, Vedder or Levy and Rowntree.

Young and Tudhop[11] have shown that emetin is a protoplasmic poison, acting equally on all tissues of the body, the actual cause of death being heart failure. Digitalis, or other heart stimulants will not lessen this toxic action on the heart when once it has been established, as was shown electrocardiographically by Berman and Leake.[12] Thus, once we have passed the minimal lethal dose, we are powerless in an attempt to apply an antidote. Fortunately, very few individuals manifest a susceptibility to emetin, for the minimal lethal dose often is not considered, in the course of treatment of amœbic dysentery.

The action of emetin on amœbæ has not been satisfactorily established. Laidlaw, Dobell and Bishop[13] have experimentally succeeded with a simple liquid medium in killing *in vitro* four strains of Entamœba histolytica in a 1 to 5,000,000 solution of emetin, within four days, provided that the medium did not become too acid. This differed radically from the results of their previous investigations,[14] when they found that emetin exhibited no characteristically high toxicity for amœbæ, and believed that the therapeutic efficacy of emetin was a result of its action upon the host, rather than upon the parasite. Failure in their previous investigations lay in the fact that the egg-serum media of Boeck and Drbohlav had been used. This result confirms the view that the therapeutic efficacy of emetin in human amœbiasis is probably due to the direct toxic action of the alkaloid on the amœbæ. Willmore[15] and others, however, have shown that there remains a considerable group of cases in which emetin is useless, no matter in what form or manner it may be employed. It was for these emetin-resisting forms of amœbæ, that yatren was originally introduced by Meuhlens and Menk.[16]

Conclusions. 1. Emetin is a protoplasmic poison acting on the host as well as on the parasite, and there is no established course of treatment with this drug that can be accepted with impunity.

2. The minimal lethal dose of emetin has not been satisfactorily determined for man. Conclusions drawn from laboratory animals are not applicable, due to differences of species and of individual susceptibility.

3. Death due to the cumulative action of emetin can occur without the advent of sufficiently severe symptoms to warn the physician before the minimal lethal dose has been passed.

4. Cases of susceptibility to emetin cannot be recognized in advance, and each case must be considered as a possibly susceptible individual to prevent the occasional cases of fatal emetin poisoning.

5. Emetin in much less than the minimal lethal dose for man is amœbacidal, and emetin in very small doses, with frequent and sufficiently long rest periods, should be employed. Failure on this basis to clear up the infection, indicates emetin-resisting strains of amœbæ, and other forms of treatment must be devised to cure the disease.

6. Our knowledge of the action of emetin on the human system at the present time, is but poorly understood. Neither do we definitely know its action on amœbæ.

7. There is no known antidote for emetin poisoning.

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CAUSES OF DEATH IN CHRONIC INTESTINAL OBSTRUCTION: A STUDY OF NINETEEN CASES.

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Stimulated recently by several cases of chronic intestinal obstruction with rupture of the proximal dilated bowel, we were led to review all cases of chronic obstruction autopsied in this hospital with especial attention to their mode of termination, for it had become our belief that the commonly taught causes of death in such cases have been given an improper relative importance. Of twelve standard texts of medicine, surgery and pathology, all place the most emphasis upon toxemia of absorption from stagnant fecal contents. Exhaustion and intercurrent infection are also given much prominence as terminal factors. Four of the twelve mention peritonitis, with or without perforation, but only more or less casually, after discussion of other, supposedly more common findings. A search of the *Index Medicus* for the past five years revealed no paper which, by its title, suggested any deviation from what is apparently the accepted belief.

Over a period of twenty-one years (1908 to March, 1929) there have been 1460 autopsies at the Mercy Hospital. Eighteen cases primarily chronic intestinal obstruction were found. If we add 1 case operated upon and now seemingly recovered, it gives us a series of 19 cases. The obstruction in every case was in the large bowel. Fourteen of these were due to carcinoma; 3 to adhesions; 1 was stenotic, following an acute sigmoid diverticulitis; and in one the cause was not reported. When these were brought together the result was radically different from the opinion described above.

The cases may, for our purposes, be grouped in four subdivisions as follows:

Group I. Spontaneous rupture of the dilated bowel above the site of the obstructing lesion, with resultant peritonitis, 9 cases.*

Group II. Leakage, either at the actual site of the lesion or about the site of operative intervention, with peritonitis, 3 cases.

Group III. Peritonitis without local gangrene or perforation, 3 cases.

Group IV. Death without peritonitis, 4 cases.

Comment. From the above it will be seen that the great majority (15 cases) died as the result of a generalized peritonitis, or, as in the one operative case, had a localized peritonitis at the point of rupture. Of the peritonitis cases, 8 and probably one more, showed

* One of these should be considered as probable spontaneous rupture as the actual gross perforation at the site of local gangrene was not surely present before death.

gross rupture of bowel above the obstructing lesion, either the result of pressure necrosis or of torsion and thrombosis of the local vascular supply. Incidentally, the ruptures were always some distance proximal to the lesion, often at the opposite end of the large bowel. Only one was close, being 10 cm. away. In one case three individual perforated areas were found. It is interesting also that in 2 cases of colostomy and 2 of spontaneous fistula, the supposed relief of obstruction was insufficient to prevent peritonitis. Of the remaining 6 with peritonitis, 3 showed definite leakage, while in 3 no gross escape of fecal contents could be demonstrated.

Group IV. represents the 4 of the 19 cases dying without peritonitis. One of them showed generalized metastasis of the obstructing carcinoma, 1 died of bronchopneumonia, and in the last 2, toxemia of absorption was the only conjecture that could be made, since other findings, save the obstructing lesion, were essentially negative.

Conclusions. 1. In a series of 19 cases peritonitis was, contrary to accepted opinion, by far the most common cause of death; (15 cases) in chronic intestinal obstruction.

2. Local gangrene and rupture of the dilated bowel proximal to (but often distant from) the obstructing lesion, was the most common cause of peritonitis.

3. Colostomy does not always so sufficiently relieve back pressure as to prevent the rupture of bowel, especially in cases of long-standing obstruction.

4. If such patients die of a toxemia, it is usually that of peritonitis or intercurrent infection, rather than the vague toxemia of intestinal absorption.

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REVIEWS.

THE AUTONOMIC NERVOUS SYSTEM. ALBERT KUNTZ, PH.D., M.D. Pp. 576; 70 illustrations. Philadelphia, Lea & Febiger, 1929. Price, $7.00.

IN this book Dr. Kuntz attempts a herculean task and acquits himself well. To tell the complete story of the sympathetic system, its anatomy, physiology, pathology, and relation to disease, would seem an undertaking to tax the resources of a group of authors. And yet the Reviewer, for one, is glad that Dr. Kuntz has had the courage to carry it through single-handed, for he has produced an exceedingly well-rounded, stimulating, and useful book, which has the additional merit of uniformity.

In regard to the anatomy of the autonomic nervous system he speaks with an authority gained from over twenty years of fruitful, original investigation. Furthermore, in dealing with a body system so extraordinarily complicated as this, the function of which is so bound up with the anatomical arrangement, it would seem that only a person steeped in its morphology would be likely to avoid pitfalls in considering its physiology and pathology. The physiologist should welcome the healthy discussion and criticism of many of his cherished hypotheses from a person who is so thoroughly familiar with the anatomy of the system, and who calmly and judicially applies everywhere his morphological yard-stick.

There is a wealth of worth-while discussion of recent work, with a valuable list of references. Altogether the book is a distinct contribution, and will undoubtedly prove of great value to the clinician, the physiologist, and the anatomist. E. C.

BLOOD GROUPING IN RELATION TO CLINICAL AND LEGAL MEDICINE. By LAWRENCE H. SNYDER, SC.D. Pp. 153; 28 illustrations. Baltimore: Williams & Wilkins Company, 1929. Price, $5.00.

THIS book, dedicated to Dr. Hektoen and written by a geneticist, covers all the historical, theoretical and practical phases of blood typing. Considerable attention is given to the interpretation and defense of the theory of multiple allelomorphous heredity as applied to the blood group, especially as this affects parentage and dis-

tribution of types. A very copious bibliography is appended. Many tables, charts and lists are given. The author warns particularly against faulty technique and inadequate family histories.

The book, however, is a reference work for the partly or wholly initiated and is not to be considered as a textbook or manual. This Reviewer would wish that the portion devoted to inheritance were more extensive and supplied with easily understood examples of practical or experimental genetics, for, although himself fairly familiar with modern theories and results, he feels sure that some blood-grouping workers to whom the book would be useful, may not obtain the best results because of the brevity and directness of statement. So too the position of the O factor is not always clear, as the matter is unfolded in the sections on inheritance and relationships, requiring re-reading and back-referencing.

The immunology of isoagglutination is scarcely touched, largely because students of the subject have devoted most time to the agglutinogen factors and their inheritance, and because the theory of von Dungern and others of independent paired factors is bound up with the agglutinin part of the reaction. This feature cannot be wholly ignored for the reasons that subgroups are dependent upon dilution and absorption as well as upon antigen, and because human serum may agglutinate the red cells of lower animals.

The technique described is limited to the simple slide method with sera A and B. While this is adequate for the ordinary typing, the Reviewer believes that for the most exact results in general practice of clinical medicine, especially where the recipient is in a delicate condition (purpura, septicemia and so forth), a cross agglutination should be done immediately before transfusion. And for this, the technique (fifteen-minute test or the prolonged one with washed red cells) should be described. This is the more important in the face of the warnings given by Dr. Snyder, that the condition of the donor as to health and diet must be considered. The section devoted to transfusion does not reflect a full medical viewpoint nor are the technical directions clear enough for the beginner to use.

In regard to the confusion arising from the use of the three systems of terminology—Jansky, Moss and Landsteiner—the author adopts the lettering system of Landsteiner because it affords the easy separation of the major component of the reaction, the agglutinogen, and permits clearer comparison with theories and work in inheritance. It is to be hoped that many medical men, especially surgeons, will be persuaded that the lettering system will be better than the arbitrary numbers. It has a better biological and numerical basis.

While warning against conclusions at present on the relation of certain diseases to blood types, the author urges further studies in all lines provided the technique and family history be accurate.

The ethnologic distribution and possible relationships in terms of blood groups are most interestingly told, but because of the yet

controversial character of the question, they do not lend themselves well to review at this place. The Reviewer would wish that another printing type had been selected by the publishers because the shape and spacing of the letters are not conducive to rapid reading. The figures and tables (except the last, which is too crowded) are entirely satisfactory. H. F.

DIE MENSCHENTHYMUS IN GESUNDHEIT UND KRANKHEIT, TEIL II, DAS ORGAN UNTER ABNORMALEN KÖRPERVERHÄLTNISSEN. By J. AUGUST HAMMAR. Pp. 1114; 815 illustrations. Leipzig: Akademische Verlagsgesellschaft M. B. H., 1929.

THIS is the second part of Professor Hammar's monumental work on the thymus, and deals with the structure of this organ in various diseases. The first part treated of the thymus in the normal condition, and has already been reviewed in this journal (1928, **175**, 413). In the present substantial volume are considered over 800 clinical cases, arranged according to the disease which was the cause of death. The same methods of recording the data are used as in the previous part. In each case are given weight and dimensions of the organ, with a low-power view showing relative amounts of cortex, medulla and interlobular connective tissue. There are tabulations of the results in each group. The thymus itself is relatively seldom the seat of pathological processes, so that this is a study of the reactions of the thymus, secondary to these various diseases. These changes show themselves chiefly as quantitative deviations from the normal, rather than qualitative. There is a comprehensive bibliography of 16 pages. This achievement of Professor Hammar comes at the end of twenty-five years' study, and is a great storehouse of information, obtained by quantitative methods, of the behavior of the thymus in various morbid states.
W. A.

THE IMMUNOLOGY OF PARASITIC INFECTIONS. BY WILLIAM H. TALIAFERRO, PH.D. Pp. 414; 28 illustrations. New York: The Century Company, 1929. Price, $6.00.

THIS volume presents a critical review of the mass of immunological work that has been done on infections with animal parasites. Introductory discussions of parasitism, parasitic infections, and immunological methods are followed by chapters on Serological Reactions, Their Specificity and Efficiency; Antibodies Manifested in Certain Infections with Blood Protozoa; Protective and Curative Action of Immune Serums; Cutaneous Tests; Production of Symptoms; The Cellular Basis of Immunity; Immunity in Parasitic

Infections; and Immunity Reactions in Classifying Parasites. A catalogue of the parasites considered, their common synonyms and hosts is given in an appendix. The text, is supplemented by many useful tabulations of immunological tests and reactions, and a bibliography of over seventy pages. This book offers, for the first time, ready access to an important field of research and can be employed either as a manual or for reference. The author is to be congratulated on this splendid presentation. H. R.

NURSING IN EMERGENCIES. By JACOB K. BERMAN, A.B., M.D., F.A.C.S. Pp. 160; 109 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $2.00.

THE purpose of the book is to familiarize the nurse with quick, correct measures for the care of the patient in emergencies. The directions are concise, the illustrations are particularly good and the equipment required is simple.

The author briefly and adequately described the method for carrying injured patients, treatment of hemorrhage, shock, electrical, thermal and chemical injuries, drowning, asphyxiation, a résumé of antidotes and treatment for the more common forms of drug poisoning and other emergency measures.

The fact that the book is concise and well organized, yet comprehensive, recommends it as part of the equipment of every nurse.

F. C.

THE STORY OF SAN MICHELE. By AXEL MUNTHE, M.D. Pp. 530. New York: E. P. Dutton & Co., 1929. Price, $3.75.

To those who, like Osler, feel that books about doctors have a proper place in medical reading and libraries, this autobiography of the Swedish doctor, Axel Munthe, may be heartily recommended. Most entertainingly written throughout, it begins with the author's idyllic dream of his future Capri home, then paints in vivid, forceful strokes some of the high lights of the career of a fashionable, yet unconventional, adventurous practitioner in Paris and Rome. A student under Pasteur, Charcot and Huchard, he successfully combined suggestion with rational medicine in Paris wards and writes about it like an artist and scientist. Gruesome yet compelling details of diphtheria and cholera epidemics alternate with romantic sidelights of practice or colorful descriptions of a pistol duel, a visit to Lapland, or an accident in an Alpine avalanche. Through the narrative runs a golden thread of love of animals, which charms more than an occasionally outcropping egotism repels. In places, too, it is difficult to believe that strict veracity is adhered to, but perhaps there are times when a good story should not be spoiled

for the want of a few facts. The final phase, the life at San Michele, though the least medical, is the most attractive and most sympathetically told of the lot. Fortunate the man of action who can thus preserve his worldly values. E. K.

BIBLIOTHECA OSLERIANA: A Catalogue of Books illustrating The History of Medicine and Science collected, arranged, and annotated by SIR WILLIAM OSLER, BT. Pp. 785. Oxford: At the Clarendon Press, 1929.

IT is well known that Osler's lifelong fondness for books became one of his major interests during most of his Oxford period, eventually to be manifested in a collection to illustrate the history of medicine and science. This he had decided as early as 1911 to catalogue in the novel and interesting form that we now see, as eventually completed by the editors W. W. Francis, R. H. Hill and Archibald Malloch. The 7783 items were divided by him into 8 sections: Bibliotheca Prima (1702 items), Secunda (2595), Litteraria (1310), Historica (955), Biographica (296), Bibliographica (537), Incunabula (104), and Manuscripts (102).

Though all are interesting, it is to the Prima that one naturally first turns. Here are grouped in chronologic order books by 67 of the greatest medical scientists through the ages, a group that gives a "bio-bibliographical" illustration of the evolution of science (including medicine), with 33 names in slightly subordinate rôles. Thus Item No. 1 is a 1495 edition of Lucretius' "De rerum natura" (illustrating the beginnings, that is, pre-Egyptian and Assyrian), eight other items follow under this heading, as it were, either other eiditions, translations, or books about Lucretius. After these come come 8 items of or about the book of Genesis. Later "The Greeks," for instance, starts with 9 items on Æsculapius; under Paracelsus are 5 items of his works and 35 of lives and commentaries; and so on. For such a selection, of course, no two authorities would agree, and we note occasional rather surprising inclusions and omissions. Nevertheless all must agree that the selection is a good one and has the added interest of reflecting Osler's personality.

The Bibliotheca Secunda, the largest group of the lot, holds all items that do not fit elsewhere, ranging in alphabetical order from works of ancient times that are not of prime importance to books or even articles by contemporaries and including Osler's own output.

The Bibliotheca Litteraria is a concrete evidence of Osler's interest in the avocations of physicians and his belief that medical libraries should properly include nonmedical works by physicians, and the doctor in fiction as well as strictly medical productions. Here is found the notable collection of Sir Thomas Browne's works, Rabelais, Guy Patin's letters, as well as our own Holmes, Weir Mitchell and similar medical authors.

The historical, biographical and bibliographic sections require no comment, other than that each is noteworthy if considered as one section of a private library. Still more so are the incunabula and manuscripts, fortunately for McGill acquired before the present high prices had been attained. The Introduction on "the Collecting of a Library" and the appendix on "A Record Day at Sotheby's" are first class bits of Osler's para-medical writings, while the frequent footnotes that make a catalogue raisonné of the whole are perhaps the most valuable feature of all in this prince of library catalogues. McGill University may well feel proud and fortunate in possessing the library on which it is based. E. K.

THE DIAGNOSIS OF HEALTH. By WILLIAM R. P. EMERSON, A.B., M.D. Pp. 272; 51 illustrations. New York: D. Appleton & Co., 1930 Price, $3.00.

THAT there is need for a book on the diagnosis of health is attested by the fact that despite noteworthy advances in medical science, at least one-third of the population are physically unfit. According to Dr. Emerson the prime requisites for optimum health are: absence of physical defects so that an individual may be free to gain, good health habits, proper social adjustment and normal health intelligence. The results obtained by the Author in his Nutrition Clinics in schools, colleges and large communities prove beyond reasonable doubt that good health may be achieved when minute attention is directed to these factors.

In this day of cults, fads and fancies a book such as this, written in a popular vein by a sane physician is of positive educational value to the laity. It also may be perused with profit by most physicians, particularly since Dr. Emerson has found that their own health intelligence quotient is especially low. S. L.

BOOKS RECEIVED.

NEW BOOKS.

The Medical Clinics of North America, Vol. 13, No. 5, March 1930, Chicago Number. Pp. 207; 17 illustrations. Philadelphia: W. B. Saunders Company, 1930.

Les Syndromes Douloureux de la Région Epigastrique, Vols. I and II. By RENÉ A. GUTMANN. Pp. 1140; 542 illustrations. Paris: Gaston Doin & Cie., 1930. Price, 200 francs.

Procedure in Examination of the Lungs. By ARTHUR F. KRAETZER, M.D. Pp. 125; 15 illustrations. New York: Oxford University Press, 1930. Price, $2.00.

* Reviews of titles followed by an asterisk will appear in a later number.

The Epidemiology and Control of Malaria in Palestine. By ISRAEL J. KLIGLER. Pp. 240; 32 illustrations. Chicago: The University of Chicago Press, 1930. Price, $5.00.

A detailed report of how malaria control was brought about in Palestine.

*Immunity in Infectious Diseases.** By PROF. A. BESREDKA. Pp. 364. Baltimore: The Williams & Wilkins Company, 1930.

*Reflex Action. A Study in the History of Physiological Psychology.** By FRANKLIN FEARING, PH.D. Pp. 350; 12 illustrations. Baltimore: The Williams & Wilkins Company, 1930. Price, $6.50.

*The Treatment of Skin Diseases—in Detail.** By NOXON TOOMEY, M.D. Pp. 512. St. Louis: The Lister Medical Press, 1930. Price, $7.50.

*Die Regulierung des Blutkreislaufes.** By DR. W. R. HESS. Pp. 163; 21 illustrations. Leipzig: George Thieme, 1930. Price, M. 12.

*Human Biology and Racial Welfare.** By various contributors. Edited by EDMUND V. COWDRY, PH.D. Pp. 612; 54 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, $6.00.

*Normal Facts in Diagnosis.** By M. COLEMAN HARRIS, M.D., and BENJAMIN FINESILVER, M.D. Pp. 247; 42 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, $2.50.

*Trauma Disease, Compensation.** By A. J. FRASER, M.D. Pp. 524. Philadelphia: F. A. Davis Company, 1930. Price, $6.50.

*Modern Otology.** By JOSEPH CLARENCE KEELER, M.D., F.A.C.S. Pp. 858; 105 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, $10.00.

*Oxford Monographs on Diagnosis and Treatment. Vol. VII. Variations in Blood Pressure and Nephritis.** By HERMAN O. MOSENTHAL, M.D. Edited by HENRY A. CHRISTIAN, M.D., SC.D., LL.D. Pp. 184. New York: Oxford University Press, 1929.

Oxford Monographs on Diagnosis and Treatment. Vol. VIII. Diseases of the Liver and Biliary Tract. By JOHN PHILLIPS, M.B.* Edited by HENRY A. CHRISTIAN, M.D., SC.D., LL.D. Pp. 539; 58 illustrations. New York: Oxford University Press, 1930.

Oxford Monographs on Diagnosis and Treatment. Vol. IX. Diseases of the Blood. By THOMAS ORDWAY, M.D. and L. WHITTINGTON GORHAM, M.D.* Edited by HENRY A. CHRISTIAN, M.D., SC.D., LL.D. Pp. 605; 33 illustrations. New York: Oxford University Press, 1930.

NEW EDITIONS.

Textbook of Pathology. By DKIRENDRA NATH. BANERJEE, M.B. (CAL.), M.D. (BERLIN). Pp. 646; 305 illustrations. Second edition. Calcutta: The Medical Bureau, 1929.

The inclusion of extensive sections on bacteriology, parasitology, diagnosis, etc., has made it impossible to treat any of these sections of pathology itself in an adequate manner.

Medical Gymnastics and Massage in General Practice. By DR. J. ARVEDSON. Pp. 298. Third edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1930. Price, $2.50.

Venereal Disease. Its Prevention, Symptoms and Treatment. By HUGH WANSEY BAYLY, M.C. Pp. 242; 77 illustrations. Fourth edition. Philadelphia: F. A. Davis Company, 1930. Price, $3.50.

The Normal Diet. By W. D. SANSUM, M.S., M.D., F.A.C.P. Pp. 134. Third edition. St. Louis: The C. V. Mosby Company, 1930. Price, $1.50.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Experimental Transmission of Endemic Typhus of the Southeastern Atlantic States by the Body Louse.—MOOSER and DUMMER (*J. Inf. Dis.*, 1930, **46**, 170) call attention to the fact that endemic typhus in the Southeastern states has been recognized apparently only within the last few years. This mild typhus does not depend upon imported cases, but it was shown through cross-immunity tests that the typhus of Europe and the typhus of these Southern Atlantic States are indigenously identical and that they must have a common origin with tarbardillo of Mexico. As a result of epidemiologic studies previously made, the conclusion had been reached that the disease is not transmitted by Pediculus humanus. For the purpose of the present experiment, the virus of Maxcy was put in contact with body lice reared on healthy persons in Cincinnati, where typhus is not known. The lice were then fed on a person immune to typhus. Ten days later they were emulsified and injected into the peritoneal cavity of guinea pigs and white rats. The results in all experiments were decisive. All of the lice became infected with Rickettsia prowazeki and the inoculation of the rice emulsion of the experimental animals was followed by the typical picture of endemic typhus. As a result of these experiments, the louse must be incriminated as a possible vector of typhus fever.

Blood of Normal Young Women Residing in a Subtropical Climate: Red Cells, Hemoglobin, Volume of Packed Red Cells, Color Index, Volume Index and Saturation Index.—A year ago there was reported by Wintrobe and Miller a study of the blood in one hundred apparently normal young men living in the extreme South. This work has been complemented by WINTROBE (*Arch. Int. Med.*, 1930, **45**, 287) in a study of fifty young women living in the same locality. The work was

undertaken as part of the study to determine normal blood standards and partly to determine whether or not an anemia due to climate actually exists. In this study the young women were normal female students who had had a physical examination within a year. All these women had lived in Louisiana, Mississippi and Alabama for three years. The methods of study and the technique of the blood counts are similar to those carried out with the young men. The average red cell count was found to be 4,930,000 per c.mm., 76 per cent of the subjects having counts ranging between 4,640,000 and 5,220,000. The average amount of hemoglobin was 13.76 gm. per 100 cc. of blood. The average hemoglobin coëfficient was 13.97 grams and the average volume of packed red cells was 39.55 cc. per 100 cc. The average volume coëfficient was 40.3 cc. The author concludes from his work that the results negate the generally accepted idea that there is an anemia in those who live in subtropical countries.

SURGERY

UNDER THE CHARGE OF

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Small Round-cell Sarcoma of the Bladder with Review of the Literature.—MacKenzie (*Brit. J. Urol.*, 1929, **1**, 359) writes that round-cell sarcoma of the urinary bladder is extremely rare and very seldom is more than one case seen in any one clinic. The symptoms are not different from those of any other malignant tumor of the bladder. The diagnosis is usually made by the pathologist either from a snipping or from the surgical or autopsy specimen. Metastases may occur in the regional lymph glands, but remote metastases are late and rare. Wide radical excision of the tumor is the only cure; less radical operations lead to an early local recurrence. A cure by either radium or Roentgen ray treatment has not been reported as yet. Operative results as shown by this series are extremely poor, death following shortly from continued hematuria or toxemia in the great majority of cases. One case has been cured by early radical excision. The author's case suffered from recurrence seven months after operation, but is well now four months after his second operation.

The Effect of Cholecystenterostomy on the Biliary Tract.—Gatewood and Lawton (*Surg., Gynec. and Obst.*, 1930, **50**, 40) state that the results of this series of experiments show again that infection of the gall bladder, liver and bile tracts follows cholecystogastrostomy in dogs. In this series, as contrasted to their previous series in which the common ducts were ligated and divided, there is no dilatation of the common ducts and no evidence of gross food particles, or roundworms in the lumina. Infection is definitely less when the common duct is not ligated and

divided. Such experimental differences suggest the following possible explanations for the differences between laboratory and clinical findings. From their previous experiments and from the work of Lehman, the authors had been led to believe that the stoma of a cholecystogastrostomy would close in the absence of common duct obstruction. While in their present series the stomata remained patent, the tendency undoubtedly is for contraction. The gastric rugæ acted almost like valves and probably partially protected the gall bladder from extraneous material. Many animals which were apparently healthy when sacrificed, showed very definite bacteriologic and microscopic evidence of hepatic infection. May there not be silent hepatitis in many of the patients who are clinically well? More autopsy data will probably settle this question. Finally may it not be possible that the human liver is better able to conquer biliary infection than that of the dog? It is a well-known fact that fat metabolism differs materially in the two.

Mortality and End Results of Operation for Abscess of the Lung.—Muller (*Ann. Surg.*, 1930, **91**, 361) writes that lung abscess is a serious disease, and the end result of a group of patients can only be determined a long time after treatment. External drainage of abscess is indicated after failure of conservative measures, in peripheral abscess with pleural involvement; cautery excision or lobectomy is indicated in multiple abscess and in abscess with lobar bronchiectasis. A series of cases is reported with an operative mortality of 28.5 per cent and a final mortality of 40 per cent. Fifty-six per cent of the survivors are clinically well. Two patients recovered from abscess, but still have the cough they had for many years, giving 64 per cent of satisfactory results in the survivors. Those patients who survive the operation, but who do not get permanently well, will be likely to succumb to the effects of the disease. Perhaps an increased use of the cautery method of extirpation of the diseased area done early may result in a greater percentage of ultimate cures, even though the immediate mortality may be higher.

THERAPEUTICS

UNDER THE CHARGE OF

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Different Preparations of Bismuth in Syphilis Therapy.—Although bismuth is adopted by syphilologists as a substitute superior to mercury, little is said of the action of the various preparations of bismuth in syphilis. It is a well-established fact, according to Lomholt (*Brit.*

Med. J., 1929, p. 887) that a complete cure is attained only after a prolonged course of bismuth therapy. The aim of the therapy should be to introduce into the organism the largest possible quantities without intoxication. The elimination of the metal is rather slow. Intensive bismuth treatment should not be continued long. It is essential that the preparation should be uniformly absorbed. Oral and cutaneous administration are unreliable. Intravenous injection is rather dangerous. The subcutaneously injected bismuth is irregularly absorbed and may cause an abscess. Intramuscular injection is the preferred method. In the different preparations the metallic bismuth content alone is important, provided that the organism can dissociate the bismuth. All bismuth preparations injure the muscle tissue, causing the formation of a small necrosis which is gradually replaced by granulation tissue which more or less prevents the absorption of the preparation used. Watery solutions are effective but rather painful when injected, and the administration has to be repeated frequently. Oily solutions are painless but rather slowly absorbed. Among the various preparations used in oil, bismuth salicylate seems to be one of the best. If watery solutions are selected for administration the preparation preference should be given to compounds of restricted solubility. The oxychlorid of bismuth is one of the best preparations for watery solutions. With particles of a size of 3 to 5 μ it is almost painless and very powerful. If the absorption of the preparation is complete the daily dose of bismuth metal may be fixed at about 0.5 mg. per kilo of body weight. The author used the following method of treatment in 152 cases with fresh syphilis without a single relapse. Neoarsphenamin, in doses of 60 to 70 cg., was given in a series of 5 to 6 intravenous injections and bismuth oxychlorid in watery suspension, in doses of 15 to 20 cg., in a series of 8 to 10 intramuscular injections. The total number of about 18 neoarsphenamin and 60 bismuth oxychlorid injections were given within a period of about two years. By the end of the treatment of the 152 patients only 2 showed a positive Wassermann reaction, 7 a doubtful and 143 a definitely negative test. Each case should receive individual consideration during the treatment.

The Use of Cowpox Lymph in the Treatment of Certain Skin Lesions.—On the basis of an experience extending back to 1925, GÖRL and VOIGT (*München. med. Wchnschr.*, 1929, **76**, 1669) recommend vaccination as a valuable therapeutic measure in a variety of dermatoses which are marked by the development of vesicles. They find it of particular use in the control of the more resistant form of pemphigus, in herpes zoster and in a variety of other forms of herpes. In the majority of cases of pemphigus the results of its use are dramatic, but in the cases of sepsis presenting the clinical picture of pemphigus its administration is usually without avail. It is a striking fact that in cases of pemphigus repeated vaccinations seem to fail in the production of any lasting immunity against smallpox, since each successive vaccination leads to a normal "take." In one case of pemphigus of the eye a boiled vaccine was employed with most satisfactory results. Herpes zoster is controlled in the sense that a further spread of local eruption is promptly checked. The vesicles already present dry up rapidly and above all the neuralgic pain disappears promptly. Both dermatosis herpetiformis

Duhring and acne fail to respond and erythema bullosum is benefited only in a transitory manner. Recurrent herpes, however, shows a marked tendency toward diminution of subsequent attacks under this treatment. The herpes of menstruation is especially promptly controlled.

The Prevention of Acute Cardiac Death.—Reviewing the various instances of acute cardiac death and, from them attempting to establish a method of determining those patients in whom such accident is prone to occur, MORAWITZ and HOCHREIN (*München. med. Wchnschr.*, 1929, **76**, 1075), find that the conditions of coronary sclerosis, syphilitic aortitis and old chronic myocardial disease are those most frequently resulting in sudden death. The electrocardiographic changes indicative of bundle branch block and arborization block, as well as possibly the inversion of the *T* waves in two or more leads and the occurrence of upward convexity of the *ST* line, are also significant forewarnings of sudden death. Very frequent premature ectopic beats, especially in elderly patients with chronic myocardial degeneration, also are of prognostic import. Although it is not usually possible to prove the contention, it seems more probable that such deaths are due to the sudden inception of ventricular fibrillation. Acting upon this assumption the authors have employed as a routine procedure the administration of two doses daily of 0.1 gm. each of quinidin alkaloid. Upon this régime carried out over one year they seem to have reduced the frequency of sudden death to a very marked degree; thus in the year 1927 there were 19 sudden deaths in patients proved, at autopsy, to have had coronary sclerosis or luetic aortitis, none of these patients having received quinidin. During 1928 only 7 patients died suddenly of coronary sclerosis or luetic aortitis. The authors feel that the results of this effort do not justify final conclusions but that they are strongly suggestive of the possibility of working out a fairly satisfactory preventive treatment.

PEDIATRICS

UNDER THE CHARGE OF

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Idiopathic Anemia of the Newborn Infant.—HAPP (*Arch. Pediat.*, 1930, **47**, 171) reviews cases in the literature as well as one of his own, and remarks on the similarity in the clinical factor with varying degrees of severity. These babies are born at full term and the delivery is usually normal. In some cases pallor is noted at birth or is seen during the first few days of life with a tendency to increase. This pallor is the only striking symptom and should lead to an examination of the blood. Blood study shows an actively regenerating anemia with marked reduction in red cells and hemoglobin. The white cells are usually increased in number and the differential count is normal. There may be present myelocytes. The platelet count is normal. Active regeneration is evidenced by nucleated red cells, polychromatophilia and increase in

reticulated cells. The spleen is usually slightly enlarged but there is no other glandular increase. There are no constant findings. Icterus is variable. Fragility tests have not been made in all the cases reviewed, but in one case where this test was made, the fragility of the red cells was found inceased. Untreated cases have recovered during the first year. Those treated by blood transfusions have recovered more quickly. In the author's case, recovery occurred in seventeen weeks. In none of the cases observed were there any remissions during infancy, and several of the cases had been observed for three or more years. The etiology of this condition is obscure. Tuberculosis in the mother has been mentioned as a possible factor, but of the cases reviewed, the one referred to in this paper is the only one in which this condition has actually been present. There was no anemia in the mother in any of the cases reviewed. The author feels that as a result of some unknown factor the hematopoietic function is depressed in these newborn infants and this factor is probably operative during intrauterine life. No conclusive evidence of hemolysis can be shown in these anemias. Rapid degeneration has been seen and it would seem that the hematopoietic function is definitely stimulated by blood transfusion which is suggested as the treatment of choice together with the administration of organic iron in broths and liver.

The Antirachitic Value of Irradiated Wheat.—TISDALL and BROWN (*J. Am. Med. Assn.*, 1930, **94**, 854) made interesting studies on the influence of this irradiated product upon rats and they attempt to interpret the results from the standpoint of the practicing physician. They feel most positively that irradiated wheat is not a reliable source of vitamin "D" as is cod-liver oil or irradiated ergosterol. The antirachitic potency is not sufficient entirely to prevent and certainly not to cure rickets in the amounts consumed in the average diet, therefore, they recommend that, in addition should receive cod-liver oil or viosterol. This need of an accessory source of vitamin "D" raises the question as to the value of irradiated wheat as a source of vitamin "D." In answer, the authors state that cereals are used largely for their energy-producing value and experience shows that rickets develops in its most severe forms in those infants fed large amounts of cereals and other carbohydrates. In other words cereals should be regarded as rickets-producing foods and irradiation can change them from rickets-producing foods to rickets-preventing foods, and in this lies the value of the irradiation as now performed. As three teaspoonfuls of cod-liver oil each day during the winter months do not furnish any excess of vitamin "D" of the amount necessary to prevent rickets in the average infant or young child any means that can remove the rickets-producing tendency of cereals should be of value.

New Experiences with Diphtheria Vaccination.—POCKLES (*Deutsch. med. Wchnschr.*, 1930, **56**, 46) states that among the children of Berlin who had been vaccinated against diphtheria a considerable number contracted the disease, and in some there was a fatal outcome. He thinks that this failure of vaccination is due to the fact that instead of effective subneutralized toxin antitoxin, other vaccines were used. The subneutralized toxin antitoxin was originated by von Behring and this is the product commonly used in America. In Germany its use has been

discontinued on account of the frequency of local reactions. In its place Schmidt's toxin antitoxin floccules, or a neutral toxin antitoxin have been used because these do not cause reactions. According to the author, children vaccinated with either of these two did not always develop a sufficient quantity of protective substance. He vaccinated 36 children with toxin antitoxin floccules and 13 with a neutral mixture of toxin antitoxin. He later determined the antitoxin content of the blood and it was found that only a part of the vaccinated children had a quantity of antitoxin that is necessary for protection against diphtheria. Because of the insufficiency of these two preparations the author reserved—for use in diphtheria toxoid, a toxin that is modified by treatment with formaldehyd. The advantage of this preparation is claimed to be in the fact that it does not contain antitoxin and consequently is free from heterologous serum and thus cannot cause anaphylaxis. A disadvantage of this toxoid is that it causes local reactions, especially in older children or in adults. Another objection is that the subcutaneous injection has to be repeated three times. This method has brought good results in many countries and is suggested as being worthy of consideration. Passing to the Schick test, the author points out that because it indicates the presence of minor quantities of antitoxin that are not sufficient for protection, it is not always a reliable indicator for immunity.

Symptoms of Vagotonia and Thymic Hypertrophy.—ALDRICH (*J. Am. Med. Assn.*, 1930, **94**, 1119) reminds us that the vagus is a part of the parasympathetic or bulbosacral division of the autonomic system and that its activity is normally opposed by the sympathetic division of this system. Theoretically vagotonic symptoms may be produced either by stimulation of the vagus or the parasympathetic, or by a reduction in the activity of the normal antagonist, the sympathetic. Activity of the suprarenals has a marked effect on the autonomic system, therefore vagotonic symptoms might follow diminished suprarenal activity. In this connection Marine pointed out that spontaneous involution of the cortex of the suprarenals occurs during the first two weeks of extrauterine life. He and other experimentors have produced by suprarenalectomy, conditions similar to status lymphaticus with thymic enlargement, and since status lymphaticus has been associated clinically with reduction in the suprarenal chromaffin substance, Marine suggests a significant relationship. He also assumes a close relationship to status lymphaticus as due to a lack of the epinephrin hormone in the blood which makes adequate systole of the heart and bloodvessels impossible, and points out that in death from this cause the heart is always in diastole. The report of MacLean and Sullivan is quoted, emphasizing an extremely low blood sugar in three cases dying from status lymphaticus. They hold that such a condition might result from imperfect suprarenal response to the various strains imposed on the body none will result in death in this condition. In this study the author analyzed 40 patients and he felt that the symptoms exhibited by them can be explained on the basis of spasm of smooth muscle and the vagus control and the suprarenal involution occurring in the newborn may result in both vagotonia and thymic hypertrophy. In his series of patients irradiation over the thymus seemed to be effective in relieving the symptoms.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Hypersensitiveness to Arsphenamin in Guinea Pigs—Experiments in Prevention and in Desensitization.—SULZBERGER (*Arch. Dermat. and Syphilol.*, 1929, **20**, 669). Following the investigations of W. Frei, working on the sensitization of guinea pigs with arsphenamin, the author conducted a similar series of observations to determine the sensitization mechanism in arsphenamin as a representative of the chemical group as a whole. Twenty-three guinea pigs were prepared by an intradermal injection of arsphenamin. Six of the animals received one-third of the minimum lethal dose of arsphenamin intracardially twenty-four hours after the intradermal injection. A skin hypersensitivity to arsphenamin could be observed in 16 of the 17 animals that received no intracardial injection of this kind. This hypersensitivity showed itself in 12 animals by a flaring-up of the area of injection from six to fifteen days later, and in 16 hypersensitive animals by a reaction of hypersensitivity to a second intradermal injection of arsphenamin. The second intradermal injection was administered to all the animals as a skin test thirty-one days after the first injection. In contrast to those which received no intracardial injection, the animals that had received an intracardial injection of arsphenamin at no time showed signs of hypersensitivity, in the form either of a flare-up or reaction of hypersensitivity to the skin test. The reaction of hypersensitivity differed greatly from the flare-up due, in the belief of the author, to variations of degree occurring at different times in the course of the same hypersensitivity. A second series of experiments was conducted in which the author attempted to desensitize 12 previously sensitized guinea pigs by intracardial injection fourteen days after the intradermal preparation of the arsphenamin. Of these animals, 6 received intradermal injections of arsphenamin identical with that which had achieved the prevention of sensitization when administered after twenty-four hours in the earlier experiment, while the other 6 animals received an intracardial injection of gold sodium thiosulphate. Neither of these measures was effective in desensitizing the guinea pigs and they reacted to subsequent intradermal tests with arsphenamin fully as strongly as the sensitized but not intracardially treated controls. The author emphasizes that his failure to produce desensitization does not prove its impossibility but rather that the method must be varied in further experiments. The author proposes to apply his results in guinea pigs

to the analogous conditions in human beings which include the occurrence of dermatitis following the more or less intimate contact with chemicals and the toxicodermata from drug ingestion. The author points out that his results confirm the clinical findings of previous investigators that patients having had arsphenamin dermatitis react to intradermal tests with arsphenamin much more strongly than normal persons. He agrees with Klauder that in a great many cases arsphenamin dermatitis follows an infiltration of cutaneous and subcutaneous tissues with arsphenamin and that as a practical application an effort should be made immediately to complete an injection in which such leakage occurs by the correct intravenous route. It might even be advisable to give the succeeding intravenous injection of arsphenamin in such an instance at a shorter interval than usual. The author concludes that all tests agreed much more closely in nonsyphilitic than in syphilitic cases so that a negative reaction given by any of the tests is of more value in ruling out syphilis than is a positive reaction of value in indicating syphilis.

(The word arsphenamin is used by the author to mean neo-arsphenamin.)

The Chemistry of the Blood in Diseases of the Skin.—SCHAMBERG and BROWN (*Arch. Dermat. and Syphilol.*, 1930, **21**, 1). In a series of 875 patients with miscellaneous dermatoses, the authors found no appreciable changes in the figures for blood sugar. A retention of nonprotein nitrogen, urea nitrogen and uric acid was discovered in 22.6 per cent to 47.7 per cent of their cases of eczema and pruritus (generalized). This increase of the nitrogenous constituents of the blood is due mainly to an improper diet or to some form of renal dysfunction such as a low-grade interstitial nephritis. The fact that this occurs more often in subjects who are in middle life or older favors this view. There is a normal pronounced discrepancy in the nitrogenous figures between the sexes which the author believes is partly accounted for by a general difference in diet. A study of the blood chemistry of patients with refractory dermatoses is of material aid in prescribing appropriate dietaries.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Pseudomyxoma Peritonei of Ovarian Origin.—The peritoneal neoplasm composed of pseudomucinous material, called pseudomyxoma peritonei, which is usually due to a ruptured ovarian cyst is of interest

to every gynecologist but is seldom seen in the practice of any one man. Thirty cases of this type have been observed in an eighteen year period at The Mayo Clinic as reported by MASSON and HAMRICK (*Surg. Clin. of N. America*, February, 1930, p. 61). The largest number of cases was found in patients in the sixth decade, while 80 per cent of the patients were past the age of forty years. Swelling of the abdomen and pain are the two most constant symptoms and their average duration before operation was less than a year. On examination the pelvis and abdomen are usually found to contain one or more masses. A large tense abdomen with a fluid wave of a questionable character may be the only abnormality found. They found a higher percentage of bilateral involvement in patients with ruptured pseudomucinous cystadenomata than in patients with the same type of unruptured tumors. This bilateral involvement was most marked in cases of malignant lesions and when papillomas were present. Pressure phenomena from the mucilaginous tumors play a large part in the health of patients with this disease, while pulmonary embolism and general peritonitis were the chief factors in the operative mortality. The prognosis is naturally better in cases of benign lesions. Removal of both ovaries and the appendix is urgently indicated in women who have passed the menopause. In those who have not passed the menopause it is generally desirable to save one ovary, but the surgeon should take into account the type of growth in the affected ovary. Hysterectomy is indicated in some cases, resection of the omentum in others and as much of the gelatinous material as possible should be manually removed from the abdominal cavity at the time of operation. At times the bowel and even the uterus may be perforated by the pseudomucinous tumors so that the extent of the operation will have to be decided by the type of lesions met. They believe that all cases should receive postoperative treatment by Roentgen ray and radium.

Irradiation of Vulvar Cancer.—We are inclined to agree with DE BÜBEN (*Surg., Gynec. and Obst.*, 1930, **50**, 110) of Budapest when he states that the treatment of cancer of the vulva is a most arduous task. Of the methods of treatment at our disposal he ranks radiotherapy first, not only because it can be used in advanced cases, but also because in most instances its use improves the condition or at least ameliorates the suffering and in a few cases even permanent cure has been secured. In most cases radiotherapy produces a temporary improvement and delays death; at any rate the life of the victim is made tolerable. Of 31 patients with vulvar cancer treated with radium at his clinic, 2 were free from recurrence six years later. One lived four years after treatment, 2 lived three years, 3 lived two years, 5 lived one year, 7 died within one year and in 7 the duration of life is unknown. After excision and microscopic diagnosis, patients with cancer of the vulva to be treated with radium are given a single dose amounting to 1200 to 2400 mg. element hours, if possible. Then if at control examination the effect seems to be unsatisfactory, the radium treatment is repeated in six to eight weeks. For irradiation of the lymph glands he uses Roentgen rays, a pigmentation dose being applied three times at intervals of six weeks. Patients treated with radiotherapy are instructed at the end of treatment to return for examination every three months, later

every six months. While these results are not startling it is well to remember what can be accomplished by nonoperative means, as in many cases the patients who are afflicted with this type of cancer are far from being in a satisfactory general condition to withstand the prolonged operation which is necessary to radically remove the cancer together with the regional lymph nodes.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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A Case of Abscess of the Iris.—Abscess of the iris is so rare that it is not even described in such a textbook as Fuch's. Therefore Jadavji Hansraj (*Indian Med. Gazet.*, 1929, **64**, 510) reports in detail a case recently seen in Bombay. A man, aged thirty-five years, came to the hospital complaining of pain and redness in the eye, the only cause that he could give being that he had rubbed his eye with a coarse cloth six days before. Examination showed marked ciliary injection, photophobia and lacrimation, the ciliary injection being much more marked on the side of the abscess (temporal). The cornea was absolutely clear. The temporal half of the anterior chamber was occupied by an oval, yellowish-white substance, immobile either to change of position by the patient or to pressure. The temporal half of the pupil and the portion of the iris peripheral to it was covered by the mass in the anterior chamber. Such of the iris as could be seen was slightly muddy, the crypts on the anterior surface were obliterated and the pattern was lost. The ocular tension was above normal. Vision was finger counting at one foot only; the other eye had full vision. A diagnosis of lens dislocated into the anterior chamber was made because of the color and appearance of the mass, the shape and size of it, and the increased intraocular tension with signs and symptoms of secondary glaucoma. Operation incision in the outer half of the cornea to remove the supposed lens. As soon as the anterior chamber was opened muddy colored pus together with a little aqueous humor began to ooze and the mass began to disappear. When irrigated it was found that the pus was coming from an opening in the iris. The outer layers of the iris were changed to a muddy color and formed a thin capsule for the sac which contained the pus. The eye was bandaged and treated with atropin. In addition the patient was given three injections of 100 cc. of a 1 per cent solution of mercurochrome on alternate days. The iris cleared completely except for posterior synechia. Vision is gradually improving; at present, finger counting at 4 feet. The infection must have been endogenous, probably arising from pyorrhea alveolaris; rubbing the eye traumatized the iris and an abscess, instead of mild iritis resulted.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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The Psychologist's Interest in Hearing.—"In the modern science of life the living organism has gradually revealed a greater and greater complexity—a complexity of substance as well as of function. So complicated have the body and its operations become that all who delve into its fascinating intricacies are inclined to alternate between the ardent enthusiasm of the explorer and the bewildered doubt of the lost traveler. . . In the sciences of life problems seem, therefore, to approach solution not so much by the discovery of new simplicities as by the revelation of new but enlightening subtleties." Stating that *hearing* is but a special case of the general trend, BENTLEY (*Arch. Otolaryngol.*, 1929, **10**, 282) calls attention to the fact that the particular focus of the psychologist is set on the experience of hearing sounds. The approach to this experience of hearing is considered by the author under four main headings: (1) A description of the simpler auditory experiences; (2) the relation of these experiences to the forms of energy delivered to the cochlea; (3) the relation of them also to aural structures and mechanisms, and (4) an account of various more complex auditory phenomena. The individual importance of the various fields in biologic, clinical and psychologic research is recognized; and the necessity for a common understanding and close coöperation between them is stressed.

The Localization of Sound.—"The word 'localization' as applied to sound is of psychological rather than physical origin. It deals with a sensation more than with a physical measurement. It differs from *location* in that it does not fix the position of a source of sound." Stating that with our unaided listening equipment we can obtain only a sense of direction, TUCKER (*J. Laryngol. and Otol.*, 1929, **44**, 812) calls attention to the fact that the head, as normally placed, is best adapted for listening in a horizontal plane. Sound localization is most accurate in front, nearly as accurate for the back, and least accurate at the side and for the overhead position. Normally, localization occurs by virtue of some difference in stimulus received by the two ears. There are three ways in which such variation in stimulus can arise: (1) Difference in sound intensity; (2) difference in phase of the incoming sound waves, and (3) difference in time of arrival of some corresponding portions of the sound waves received by the two ears. After discussing these theories, the author mentions certain aural methods by instruments devised for sound location of aëroplanes.

Further Experience with the Dichloramin Treatment of Mastoid Wounds.—FENTON (*Ann. Otol., Rhinol. and Laryngol.*, 1929, **38**, 657) concludes that bacteriologic examination bears out eleven years of

clinical experience in several hundred cases, demonstrating the value of dichromin-T, 2 per cent in chlorcosane, as a routine dressing in acute mastoid surgery—not only for its remarkable inhibitory action on bacterial growth but also for shortening materially the duration of postoperative treatment. The wound is left open, save for one or two sutures at the ends. It is filled with the oil which is "held in" by a lightly inserted fold of narrow oil-soaked gauze packing. The dichloramin is used daily during the first week or ten days of the reparative process.

Deafness in Syphilis: An Audiometric Study.—In a series of 2201 thoroughly studied patients on a general diagnostic service in which emphasis was laid on diseases of the ductless glands, about one-half could be classed in the nonendocrine group and more than one-third (792) were subjected to audiometric study. DRURY (*Ann. Otol., Rhinol. and Laryngol.*, 1929, **38**, 625) after an exhaustive analysis of these 792 cases, found that 81, or practically 10 per cent, of them showed a curve characterized by a marked lowering of auditory acuity at 4096 d. v.; and that in this group there was a surprising incidence of "putative or established syphilis." Emphasizing that the recognition of syphilitic auditory neuritis is of paramount importance as possible evidence of early cerebrospinal involvement, the author recommends the audiometer as the instrument of choice in the diagnosis of incipient syphilis of the auditory nerve. He further states that when this particular curve—the "dipper gap"— is encountered in a syphilitic, the aural damage is permanent, although the etiologic factor may be cured successfully.

RADIOLOGY

UNDER THE CHARGE OF

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Etiology of the Ill Health of Children Born After Maternal Pelvic Irradiation.—The cause of ill health or defects manifested by 38 or 50.7 per cent of a group of 75 children irradiated while *in utero* has been investigated by GOLDSTEIN and MURPHY (*Am. J. Roent. and Rad. Therap.*, 1929, **23**, 322), who have reported previously the effects of preconception irradiation. The ill health of 10 children of the 38 was attributed to parental influences or to accidental causes. Twenty-eight, or 37.3 per cent of the 75 children born after postconception radium or roentgen irradiation manifested mental or physical abnormalities which could not be attributed to parental influences, accidental infections, or causes other than irradiation. In this group of 28 children there were 20 who suffered severe disturbances of the central nervous system. Sixteen microcephalic children were included in this group. The remaining 8 children exhibited other serious disturbances of health

and development which may have resulted from the irradiation received while *in utero*. The large number of grave malformations appearing in children born after postconception irradiation, the uniformity of these deformities (chiefly microcephaly and mental defects) strongly indicate that there is a distinct relation between the irradiation and the defects. The occurrence of two cases of microcephaly and one of hydrocephaly in children born of women irradiated after the fifth month indicates the danger of irradiation of the fetus in the advanced stages of development. It is the belief of the writers that therapeutic pelvic irradiation during pregnancy is extremely likely to injure the growing embryo, and may result in the birth of a seriously defective child. On the other hand, they find no indication that irradiation for diagnostic purposes during pregnancy is deleterious in any way to the health of the offspring.

Treatment of Malignant Tumors of the Rectum by Radium and Roentgen Rays.—Bowing, Fricke and Smith (*Radiology*, 1929, **13**, 443) report the results in 127 cases of malignant disease of the rectum treated at The Mayo Clinic with radium and Roentgen rays. The majority of the cases were inoperable, due to the size and extent of the primary lesion, or local metastasis, metastasis to important viscera or patient's poor general condition. Adenocarcinoma of moderate malignancy predominated. Twenty-three per cent of the patients lived from three to six months, 18 per cent from six to nine months, and 34 per cent longer than nine months. Almost 4 per cent survived eighteen to twenty-four months, and slightly less than 3 per cent lived twenty-four months or more. The writers regard it as evident that the lives of these patients were prolonged and that the activity of the disease was reduced thus diminishing distressing complications. Improvement noted consisted largely in lessening of rectal discharge and pain, reduction of the size of the tumor and cessation of bleeding.

Influence of Phenolphthalein on Intestinal Movements.—From their roentgenologic studies Caldwell and Crane (*Radiology*, 1929, **13**, 403) offer the following conclusions: Phenolphthalein in ordinary dosage has no appreciable effect on the movements of the stomach or the small intestine. Phenolphthalein does not directly affect the rate of movement, in any part of the digestive tract, of the food material taken simultaneously with it. The proximal half of the colon shows very little, if any, increase in its motor activity during the period in which phenolphthalein is most active, about eight to twelve hours after it is taken. The movements of the distal half of the large intestine are strongly stimulated by phenolphthalein during its active period. Phenolphthalein has no local effects in any portion of the alimentary canal due to chemical or mechanical action on the bowel wall. The drug is in part absorbed during its passage through the small intestine and reexcreted into the colon or large bowel. The laxative properties of phenolphthalein are due chiefly if not entirely to a stimulation of the large bowel by that portion of the drug which is absorbed and carried by the blood to this portion of the tract. Only that portion of the intestinal contents which has reached the distal colon by the time the phenolphthalein becomes active, namely, about eight to twelve hours after its ingestion, is directly influenced by it. Other apparent effects are secondary and indirect.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Etiology of Epidemic Encephalitis. Its Relation to Herpes, Epidemic Poliomyelitis and Postvaccinal Encephalopathy.—LEVADITI (*Arch. Neurol. and Psychiat.*, 1929, **22**, 767) reviews in very clear sequence the modern researches in relation to the etiology of epidemic encephalitis and its relation to herpes. He feels that his own researches have established the following facts: Inoculation of laboratory animals with encephalitic material by the most various routes surprisingly seldom gives positive results; direct transmission of the virus from man to animal has been secured only in the rabbit; after successful transmission to one rabbit the virus can be maintained successfully by regular passages through the animals of the same species; he believes also that his previous researches had seemed to clear up some of the characteristics of the encephalitic virus, the clinical and anatomopathologic aspect of the infection in the various receptive species, the routes by which the virus penetrates, its distribution in the organism, how it is eliminated, immunity, the problem of germ carriers, and some other points. Following this period in the research the author was successful in producing keratitis by corneal inoculation which gave rise also to typical clinical and pathologic pictures of experimental encephalitis. Prior to 1920 certain German research workers by experimenting with herpetic keratitis came to the conclusion that herpes was a specific infectious disease produced by a virus which was probably invisible and filtrable and was virulent for the rabbit. Later Doerr and Vöchting observed disturbances similar to encephalitis in rabbits in their experimental animals suffering from herpetic keratitis, thus demonstrating an invasion of the central nervous system by this virus. This led to the conception of the identity in nature of the virus of encephalitis and the virus of herpes. The author gives the credit for this to Blanc. Experiments in cross immunization were then undertaken and led to the conclusion that the two viruses were either identical or very similar, the chief differences being on the one hand a greater cutaneous affinity and on the other hand a greater cerebral affinity. Subsequent researches have been both nonconfirmatory and confirmatory. The principal objections to the nonconfirmatory researches have been a confusion of epizoötic encephalomyelitis in the rabbit with encephalitis produced by the herpeticoencephalitic virus. These two conditions can be differentiated clinically and pathologically, hence the majority of the nonconfirmatory experiments can be discarded. The confirmatory researches have established certain encephalitic strains of the herpetic

type as follows: Levaditi and Harvier strains of cerebral and nasopharyngeal origin; the Doerr and Schnabel strain from the cerebrospinal fluid of an encephalitic patient; the Doerr and Berger strain from the neuraxis of a case of epidemic encephalitis diagnosed by microscopic examination; the Berger strain by inoculation of glycerinated encephalon into rabbits; the Schnabel strain from the cerebrospinal fluid of a case of acute encephalitis; the Luger and Lauda strain from cerebrospinal fluid; the Hogander strain from glycerinated encephalon; and some other strains not so fully studied. The author considers his own researches confirmed and that the total researches up to this time lead to the following conclusions: The transmission of encephalitis from man to rabbit is extremely difficult; rabbits that resist the original inoculation are found to be free from lesions and their sensitivity to inoculation from a previously infected animal is as great as that of rabbits not previously inoculated, so that their resistance to the first inoculation is not due to natural immunity; all the strains so far isolated and studied by the author and his collaborators have been keratogenous, are virulent for the guinea pig and the mouse and nonpathogenic for the dog, and cross immunity shows the identity and nature of the strains with the herpetic virus. Hence, the author believes that the virus of herpes as the chief etiologic factor of von Economo's disease has been entirely confirmed. The chief objection to this, be believes to be the contention that the presence of the herpetic virus in the neuraxis of encephalitic subjects is not an absolute proof that it plays an etiologic part in von Economo's disease since it might be a common organism associated with the still unknown virus of encephalitis. The author cites a number of observations that materially reduce the probability of this being the case. In researches as to predisposition and virulence in experiments on monkeys the author found that the monkey is, as a rule, refractory to the encephalitic virus isolated from, and maintained by passages through the rabbit even when the virus is introduced direct into the encephalon. Certain monkeys he found to be exceptions to this rule which he attributes to impairment of their natural resistance. He compares this with observations made on man and believes that simian and human species are not capable of contracting encephalitis unless for special reasons the natural refractory state proper to these species is impaired. On this basis he accounts for the discrepancy between the frequency of herpes and the rarity of encephalitis. Moreover, the author was able to produce typical encephalitis in a monkey by intracerebral inoculation of an herpetic virus. He discusses at length variations in the neurotropic, corneotropic and dermatotropic affinities of the various strains. In conclusion, he does not believe that the etiologic problem of epidemic encephalitis is completely solved, nevertheless, a great deal of progress has been made and the identity of encephalitis virus with that of herpes has been fairly well established.

Habitus Lipodystrophicus with Affective Psychosis—(Hypomanic Excitement).—WERTHAM (*Arch. Neurol. and Psychiat.*, 1929, **22**, 714) would reserve the term habitus lipodystrophicus for those types (so far found only in women) in which there is a marked incongruity in the fat deposition of the upper and lower parts of the body, usually showing marked thinness above the waist line combined with marked obesity

below. He reports a case of this type which showed a typical hypomanic excitement. In discussing the case he shows that the patient falls within the upper limit of the pyknic body type but nearer the range of values found in cases which belong to neither the pyknic nor the asthenic group. He believes that the lipodystrophic habitus is constitutionally connected with lipodystrophia progressiva, the etiology of which is as yet unclear, but which seems to have a constitutional pathogenic factor. He comments on the fact that dysplasias of any type are relatively uncommon in affective psychoses and considers the case reported here as of special interest for this reason.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Types of Tubercle Bacilli in Human Tuberculosis.—GRIFFITH (*J. Path. and Bact.*, 1929, **32**, 813) reviews much of the English as well as some of the foreign literature and reports the more recent researches of himself and his colleagues on this subject. An analysis of their results is considered in the three age groups of four years and under, five to fourteen years, and over fourteen years of age. In the English series of specimens. of 116 cases of cervical gland tuberculosis 3 were of human, and 18 of bovine origin in the first age group; during the second period 28 were of human and 26 of bovine type; 32 were of human and 9 of bovine origin in the third age group. The total bovine incidence of cervical adenitis at all ages was 45.7 per cent. Among 511 cases of bone and joint tuberculosis 60 were of human and 24 of bovine type during the first period, 277 were of human and 65 of bovine during the second period, and 81 were of human and 4 of bovine origin during the last period. The total bovine incidence in the bone and joint disease group was 18.2 per cent. Of 23 cases of urogenital tuberculosis none occurred under four years; in the second age group 2 human and 1 bovine strain were encountered; after fourteen years of age 17 cases were of human and 3 of bovine origin. The total bovine incidence of urogenital tuberculosis was 17.4 per cent. In 33 cases of meningeal tuberculosis studied, 2 were of human and 1 of bovine type during the first period, 13 of human and 7 of bovine in the second period, while 9 human and 1 bovine strain were met with in the last age group. The total bovine incidence of meningeal disease was 27.3 per cent. Material taken from 183 autopsies yielded 72 human and 29 bovine types in the first age period, 48 human and 7 bovine in the second, and 21 human and 1 bovine in the third. The total bovine incidence in the autopsy group was 22.3

per cent. In the Scottish series of specimens, of 17 cases of cervical gland tuberculosis 1 human and 3 bovine strains occurred in patients under four years, 3 human and 7 bovine between five and fourteen years, and 1 human and 2 bovine after the latter age. The total bovine incidence in this group was 70.6 per cent. Bone and joint tuberculosis occurred in 30 of the Scottish cases, 12 human and 6 bovine strains being represented in the first age group, 8 human and 2 bovine in the second, and 2 human but no bovine in the third. The total group bovine incidence was 26.6 per cent. Considering the distribution of the primary lesions as a criterion it appeared in the author's investigations that the bovine bacillus enters the body exclusively by way of the alimentary tract while the respiratory tract appeared to be the chief portal of entry for the human bacillus. Evidence is advanced to show that demonstrable tubercle bacilli from foci presenting an inactive appearance at autopsy must frequently be dead as inoculation of material from these areas into susceptible animals meets with negative results. Tuberculous lesions whether produced by human or by bovine tubercle bacilli, and wherever situated, may undergo spontaneous arrest and cure.

The Distribution of Colloidal Lead in the Tissues After Its Intravenous Injection.—DILLING and HAWORTH (*J. Path. and Bact.*, 1929, **32**, 753) have followed by histologic and chemical methods the fate of therapeutic forms of colloidal lead used by the Liverpool Medical Research Organization in the treatment of malignant disease. The doses, given intravenously, which were injected into cats in divided amounts over a period of three to four hours, were massive, varying between 0.3 and 0.5 gm. lead; while those given to rabbits by a single injection usually represented 0.025 to 0.05 gm. of lead. The authors found the lead concentrated first in the spleen where it had entered the splenic cells, the large phagocytic cells and more rarely the endothelium of the splenic vessels. Large amounts were also found early in the parenchymal and Kupffer cells of the liver and in the alveolar cells of the lung. In animals killed twenty-four hours after an injection, there was less lead in the spleen while particles were present in larger numbers and in more uniform distribution in the hepatic and Kupffer cells. The particles in the lungs, after this period, had largely disappeared from the alveolar walls and were contained in leukocytes in the intra-alveolar septa. No evidence of injury to the liver, lung, or spleen by the lead was observed. In the kidneys the granules were distributed within the glomeruli and around the secreting tubules, less frequently along the collecting tubules. These organs showed microscopically some swelling and degeneration of the secreting cells in the cortical tubules with loss of nuclear staining; in some cells necrosis was apparent. Although the lead was observed to be concentrated chiefly in the cells of the reticuloendothelial system, chemical examination revealed its widespread presence in various tissues. Excretion occurred into the urine, the bile, and the alimentary tract.

Etiology and Pathology of Primary Lung Tumors.—SCHUSTER (*J. Path. and Bact.*, 1929, **32**, 799) notes the increasing incidence of lung tumors and reports the investigation of 62 cases of pulmonary neo-

plasm. In this group there were 8 cases of sarcoma, lymphadenoma and thymic tumor and 54 cases of carcinoma. The author classifies the carcinomatous growths as: (1) Tumors arising from the bronchial structures, composed of epithelium which may be high columnar, or spindle in shape, or of polymorphic character including squamous and polygonal cells. (2) Small cell tumors composed of cells of round, oval, cubical, or small columnar shape, probably of bronchial origin and frequently metastasizing to brain. (3) Tumors from the alveoli. The existence of alveolar carcinoma has not been proven. The pulmonary tumors metastasized most frequently to lymph gland, liver, suprarenal gland, and brain, but widespread and numerous metastases were not common. The persistent presence of columnar cells and mucin in the various tumors suggested the bronchial lining as the common site of origin of pulmonary neoplasm but it was impossible to distinguish histologically between tumors which arose from the bronchial epithelium and those which arose from the glands and their ducts. No definite etiologic factor in the incidence of these growths could be demonstrated and pneumokoniosis did not appear to be a cause.

HYGIENE AND PUBLIC HEALTH

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Endemic Typhus Fever of the Southeastern United States: Reaction of the Guinea Pig.—Maxcy (*United States Pub. Health Rep.*, 1929, **44**, 589) gives the following discussion and summary after reciting the details of his studies: Blood from persons sick with the "endemic typhus" of Southeastern United States injected into guinea pigs produces a definite febrile illness, with recovery and subsequent immunity to reinoculation. The reaction of the guinea pig appears to be identical with that produced by Mexican typhus, according to Mooser's description. It differs from that of the Old World typhus: (1) in regard to the character of the fever curve; (2) in the relative rarity of the so-called typhus nodes in the histologic preparation of the brain; (3) in the presence of an obvious and well-defined scrotal lesion first described by Neill in 1918 in Mexican typhus. So far as the differences in the temperature curve and in the relative frequency of occurrence of typhus nodes are concerned, these might be explained as due to strain variation. In a study of 13 strains obtained from cases in the same general locality in Poland, Hach (1925, *b*) found one strain in which, in spite of a very outspoken febrile reaction, the brain lesions were extremely hard to find.

In another the temperature elevations were relatively slight, although the period of incubation and duration of the fever were essentially the same as in other strains. On the other hand, the involvement of the scrotum is much more striking and extensive than has been observed or described in guinea pigs inoculated with Old World typhus. When this obvious involvement was first encountered in a strain obtained from a case in Montgomery, Alabama, in 1925, it was thought possible that it might be due to a secondary or contaminating infection. Since that time the same finding has been present in three other strains which have been successively established from cases in Montgomery, Ala., Savannah, Ga., and Wilmington, N. C. It was observed by Dr. William Allan in a strain from a case in Charlotte, N. C. (personal communication). It has been constantly associated with the presence of the virus and not with other infections in guinea pigs. It has not been observed during the past two years in guinea pigs from the same stock which have been inoculated with two strains of Old World typhus, though much less extensive histologic changes of a similar nature occur. These findings have been so consistent that it seems to be established that the obvious involvement of the scrotum and the rarity of brain lesions are characteristic of the endemic typhus virus in guinea pigs as they are of Mexican virus. The demonstration of rickettsia-like organisms in the epithelial cells of the tunica brings additional evidence as to their identity.[1] It appears, therefore, that a North American strain of typhus can be recognized and distinguished from Old World typhus, though the two be closely related immunologically. The conclusion may be drawn that the disease which is endemic in our eastern seaports, Wilmington, N. C., Charleston, S. C., Savannah, Ga., Jacksonville, Fla., belongs to the typhus group, but is not dependent upon importation from across the sea. This disease has a common origin with the typhus of Mexico, even though transmission be effected by some agent other than that generally recognized for this disease, namely, the louse.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 21, 1930

The Influence of Carbon Dioxid Upon the Respiration of Unicellular Organisms.—WALTER S. ROOT (from the Department of Physiology, University of Pennsylvania, the Marine Biological Laboratory, Wood's Hole, Mass., and the Department of Physiology, Syracuse University). The respiratory exchange of Paramecium caudatum and the fertilized eggs of Arbacia punctulata have been studied by the methods of gas analysis.

At 15-mm. Hg. carbon dioxid tension the rate of oxygen consumption

[1] More recently, Dr. Henry Pinkerton, of the department of pathology, Harvard University (personal communication), has succeeded in demonstrating these minute intracellular organisms in the scrotal sac of guinea pigs infected with European typhus, even though the reaction be scarcely visible macroscopically.

of paramecia increases, reaching a maximum of 13 per cent above the control at 40 mm. At higher tensions the rate of oxygen consumption steadily decreases, crossing the control line at 66 mm. The average respiratory quotient in forty-eight controls was 0.623. The average value in forty-two carbon dioxid experiments was 0.961. The respiratory quotients increase as the tension of carbon dioxid increases, because the rate of carbon dioxid production remains relatively constant up to a carbon dioxid tension of 425 mm. Hg.

The rate of oxygen consumption and carbon dioxid production of fertilized arbacia eggs is decreased from the beginning in a linear relation to 30 per cent of the control at a carbon dioxid tension of 35 mm. Hg. At this point the curve bends sharply, falling as a straight line to 20 per cent of the control at 180 mm. Hg. The average respiratory quotient in thirty-two control experiments was 0.711. The average value in twenty-six carbon dioxid experiments was 0.676.

Carbon dioxid causes an initial increase in the motility of paramecia followed by a decrease (personal communication from Mr. Orren Chase). It is suggested that the initial rise in the rate of oxygen consumption observed in the presence of carbon dioxid is dependent upon this increased motility.

The Rôle of Copper in the Setting and Metamorphosis of the Oyster.—H. F. PRYTHERCH (assistant aquatic biologist, U. S. Bureau of Fisheries). The most important and critical period in the life history of the oyster is that during which the fully developed larva cements itself to some clean, firm surface such as old shells or stones and then undergoes a metamorphosis into a spat and adult oyster. The term setting is applied to this process of attachment, which is a biologic reaction of a most positive character. A study of the setting reaction under natural conditions showed that it occurred during the low-water stage of the tide or, in other words, when river discharge had its greatest effect on the physical and chemical condition of the water over the oyster beds. The environment of the oyster is the most complex, from a physical and chemical standpoint, of any on the globe, and at periods of low tide we find the extremes of many factors, as the mixing of fresh and salt water is taking place. Experiments with the oyster larvæ under controlled laboratory conditions showed that changes in temperature, salinity, hydrogen-ion concentration, oxygen content, CO_2 tension, and water pressure would not, in a single instance, induce the setting reaction. However, if in reducing the salinity, river water was used instead of distilled water, the larvæ gave a positive setting reaction which indicated that there was some substance in the river water which served to stimulate and control their attachment and metamorphosis. Further experiments involving variations in the amount and proportion of the cations and anions of the neutral salts were found to be ineffective in producing setting of the larvæ as were also the compounds of iron, zinc, tin, lead, aluminum and silver. The only element that produced a positive setting reaction was copper in the form of a pure metal or as a carbonate, sulphate, or chlorid. This heavy metal was effective in concentrations of one part copper to 5 million or 10 million parts of sea water and it initiated the setting process almost immediately. In the river water, copper was found to be present in relatively this same amount and it is the specific element that is necessary for the attach-

ment, metamorphosis and survival of the oyster. River water from which the copper had been removed by precipitation and filtration was no longer effective in producing setting.

Cytologic studies of the larva showed that during its development there were gradually being deposited near the liver two dark green pigmented bodies which disappeared with its metamorphosis into the adult form. These pigment spots on closer examination were found to consist of a mass of densely packed leukocytes containing numerous green-colored granules. When the setting reaction begins the pigment spot breaks up rapidly, as approximately 300 leukocytes migrate from each into the blood steam, and by greatly increasing its oxygen-carrying capacity supply an effective mechanism for the rapid growth and development which follows. The rate of growth of the larva and its metamorphosis were found to be controlled largely by its ability to obtain this essential element in the form of free metal ions when the mixture of salt and fresh water is taking place.

Since copper plays such an important rôle in the respiratory processes of the oyster, it is to be expected that growth and development of the organism will be controlled to a large extent by the presence and availability of this important element in its environment.

The Mechanism of Curarization.—W. A. H. Rushton (from the Johnson Foundation for Medical Physics, University of Pennsylvania). There are many conditions which abolish conduction from nerve to muscle, although neither individual tissue has lost its conductivity. This state is curarization in the broad sense of the word, and two mechanisms have been proposed to account for it. Claude Bernard postulated a susceptible intermediate substance whose conductivity was abolished earlier than that of muscle or nerve. Lapicque postulated that conduction was only possible between tissues of approximately the same chronaxie, and that curarization is due to the alteration of the time relations of one tissue relative to the other.

In a previous communication to this society evidence was given suggesting strongly that the nerve-muscle complex contains two excitable substances of very different chronaxies. The substance isochronous with nerve was identified with the intramuscular nerve twigs, whereas the chronaxie of the muscle substance itself was some twenty times as great. If this is true, Lapicque's theory of curarization would require that impulses could not pass from nerve to muscle even under normal circumstances.

The effects of curare and of fatigue through the nerve were the same and as follows: The substance identified with muscle suffered no change in threshold for any duration; that identified with nerve twigs was abolished at the same time as the failure of excitation through the nerve, and a typical muscle curve was revealed in its place. These results confirm the former identification of the two excitable substances in muscle, and confirm Claude Bernard by showing that curarization occurs when there is no excitability change at all of the muscle substance.

Lapicque's experiments upon the antagonism of strychnin and veratrin were repeated, but his results were not confirmed. Strychnin cause a rise in nerve threshold but no change in chronaxie, nor was it ever observed to restore indirect excitation which had been abolished by veratrin.

Mercury Derivatives of Cystein.—JAMES C. ANDREWS and PAULINE D. WYMAN (from the Department of Physiological Chemistry, University of Pennsylvania). The method of preparing cystein described by HARRIS (*Proc. Roy. Soc.* (Lond.), Series B, 1913, **94**, 441) has been shown by ANDREWS (*J. Biol. Chem.*, 1926, **69**, 209) to result in only about 85 per cent reduction. The method consists in precipitating cystein with mercuric sulphate and treating the compound formed with hydrogen sulphid. Mercuric sulphid is precipitated and the greater part of the cystin is reduced to cystein. Since cystin alone in acid solution is not reduced by hydrogen sulphid, the reduction occurring when the mercuric sulphate compound is used has been attributed to some catalysis inducted by the simultaneous precipitation of the HgS and liberation of the free cystin. In such a case the reaction involved should be:

$$2H^+ + S^= + RSSR^{++} \rightarrow 2RSH^+ + S^\circ$$

that is, free sulphur, equivalent to the cystin reduced should be precipitated along with the HgS. However, repeated attempts to identify free sulphur in the precipitate have always failed.

Our investigations of the composition and properties of this mercuric sulphate compound also brought out several facts which were not explainable on the assumption that the compound was one of cystin and mercuric sulphate. For example, analysis showed the compound to contain 3 atoms of mercury to 2 of nitrogen (corresponding to 3 mercury to 1 cystin) whereas potentiometric titration of cystin with mercuric sulphate solution gave a sharp minimum on the voltage curve at a ratio of 1 mercury to 1 cystin.

Similar investigations by VICKERY and LEAVENWORTH (*J. Biol. Chem.*, 1930, **86**, 129) with silver salts, led them to conclude that when silver salts react with cystin the precipitate formed is silver cystein instead of silver cystin, and that the cystein is formed by a mutual oxidation-reduction reaction of the Canizzaro type whereby cysteic acid is the oxidation product. In testing this suggestion in the light of our results with mercury we find surprisingly good confirmation. If the precipitate obtained from mercuric sulphate on cystin already represents the reduced compound, no free sulphur should be formed. The 1 to 3 cystin to mercury ratio represents equally well a 2 to 3 cystein to mercury ratio with 1 mercury substituted for the 2 hydrogen atoms of the sulphydryl groups of 2 cystein molecules and the other 2 mercury atoms added to the two amino groups. This structure fully explains the potentiometric results: the introduction of the first mercury atom is accompanied by reduction of cystin to cystein, the other 2 mercury atoms are merely additive. Hence only the first would cause a break in the voltage curve.

Filtrates from the precipitation of 1 cystin with excess mercuric sulphate have always been dextro-rotatory. This supports the hypothesis of cysteic acid which has the value:

$$[\alpha]_D = +8.25$$

The hypothesis of a mutual oxidation-reduction whereby cystin is simultaneously oxidized to cysteic acid and reduced to cystein is of decided biologic interest in connection with the formation of taurin in the body.

Editor's Statement.

We announce with regret that it has just been brought to our attention that in the article by Carlo J. Tripoli on "A Study of Stools Cultured for Endameba Histolytica for Diagnostic and Other Purposes" in the December, 1929, number of The American Journal of Medical Sciences (vol. **178**, p. 822) several extensive statements occur that had previously appeared in articles by Drs. Clifford Dobell and P. P. Laidlaw (in *Parasitology*, 1926, **18**, 283), and by Dr. J. H. St. John (*Am. J. Trop. Med.*, 1926, **6**, 319), copied either *verbatim* or with the change of a few words in the course of several sentences. These repetitions were not enclosed in quotation marks, nor was their source acknowledged in any way, except that the original authors' names and articles were included in the list of references. Communication with Doctor Tripoli and those under whom the work was done indicates that the work was primarily prepared as a class exercise and that the author—a medical student at the time—wrongly considered it legitimate to make even lengthy excerpts from the articles of others if reference to the articles was made in the bibliography. The minor textual changes were made by those to whom the manuscript was shown, who, like the editors, were unaware that the material had been copied.

We wish to express to Drs. Clifford Dobell and P. P. Laidlaw, and to Dr. J. H. St. John our deep regret that parts of their articles should have thus appeared in our Journal without the customary proper acknowledgment.

Notice to Contributors.—Manuscripts intended for publication in the American Journal of the Medical Sciences, and correspondence, should be sent to the Editor, Dr. Edward B. Krumbhaar, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

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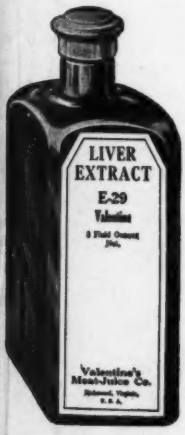

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